1261203

THE UNITED STATES OF AMERICA

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United States Patent and Trademark Office

*December 14, 2004*

**THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.**

**APPLICATION NUMBER:** ***60/509,882***
**FILING DATE:** ***October 08, 2003***
**RELATED PCT APPLICATION NUMBER:** ***PCT/US04/33349***

Certified by

Jon W Dudas

Acting Under Secretary of Commerce
for Intellectual Property
and Acting Director of the U.S.
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04772 - U.S. PTO

00746 U.S. PTO 60/509882 100803

Practitioner's Docket No. 59752-P (70207) *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Peter C. **MELTZER** and Bertha Kalifon **MADRAS**

For: **PYROVALERONE ANALOGUES AND THERAPEUTIC USES THEREOF**

**Mail Stop Provisional Patent Application**
**Commissioner for Patents**
**P.O. Box 1450**
**Alexandria, Virginia 22313-1450**

## COVER SHEET FOR FILING PROVISIONAL APPLICATION (37 C.F.R. § 1.51(c)(1))

*WARNING: "A provisional application must also include the cover sheet required by § 1.51(c)(1) or a cover letter identifying the application as a provisional application. Otherwise, the application will be treated as an application filed under paragraph (b) [nonprovisional application] of this section." 37 C.F.R. § 1.53(c)(1). See also M.P.E.P. § 201.04(b), 6th ed,. rev. 3.*

*NOTE: "A complete provisional application does not require claims since no examination on the merits will be given to a provisional application. However, provisional applications may be filed with one or more claims as part of the application. Nevertheless, no additional claim fee or multiple dependent claims fee will be required in a provisional application." Notice of December 5, 1994, 59 Fed. Reg. 63,951, at 63,953.*

*"Any claim filed with a provisional application will, of course, be considered part of the original provisional application*

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**CERTIFICATION UNDER 37 C.F.R. § 1.10***
*(Express Mail label number is mandatory.)*
*(Express Mail certification is optional.)*

I hereby certify that this correspondence and the documents referred to as attached therein are being deposited with the United States Postal Service on **October 8, 2003**, in an envelope as Express Mail Label No. **EV 343 732 845 US** addressed to Mail Stop Provisional Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Lee Dunkle
*(type or print name of person mailing paper)*

Lee Dunkle
**Signature of person mailing paper**

*WARNING: Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. § 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

**WARNING: Each paper or fee filed by "Express Mail" must have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. § 1.10(b).*
*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will not be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

*disclosure." Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,209.*

NOTE: *"A provisional application is not entitled to the right of priority under 35 U.S.C. 119 or 365(a) or § 1.55, or to the benefit of an earlier filing date under 35 U.S.C. 120, 121 or 365(c) or § 1.78 of any other application. No claim for priority under § 1.78(a)(3) may be made in a design application based on a provisional application. No request under § 1.293 for a statutory invention registration may be filed in a provisional application. The requirements of §§ 1.821 through 1.825 regarding application disclosures containing nucleotide and/or amino acid sequences are not mandatory for provisional applications." 37 C.F.R. § 1.53(c)(3).*

NOTE: *"No information disclosure statement may be filed in a provisional application." 37 C.F.R. § 1.51(d). "Any information disclosure statements filed in a provisional application would either be returned or disposed of at the convenience of the Office." Notice of December 5, 1994, 59 Fed. Reg. 63,591, at 63,594.*

NOTE: *"No amendment other than to make the provisional application comply with the patent statute and all applicable regulations, may be made to the provisional application after the filing date of the provisional application." 37 C.F.R. § 1.53(c).*

**WARNING:** *A provisional application may be abandoned by operation of 35 U.S.C. 111(b)(5) on a Saturday, Sunday, or Federal holiday within the District of Columbia, in which case, a nonprovisional application claiming benefit of the provisional application under 35 U.S.C. 119(e) must be filed no later than the preceding day that is not a Saturday, Sunday, or Federal holiday within the District of Columbia. Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,202.*

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C.F.R. § 1.51(c)(1)(i).

**1.** The following comprises the information required by 37 C.F.R. § 1.51(c)(1):

**2.** The name(s) of the inventor(s) is/are (37 C.F.R. § 1.51(c)(1)(ii)):

NOTE: *"If the correct inventor or inventors are not named on filing, a provisional application without a cover sheet under § 1.51(c)(1), the later submission of a cover sheet under § 1.51(c)(1) during the pendency of the application will act to correct the earlier identification of inventorship." 37 C.F.R. § 1.48(f)(2).*

NOTE: *"The naming of inventors for obtaining a filing date for a provisional application is the same as for other applications. A provisional application filed with the inventors identified as 'Jones et al.' will not be accorded a filing date earlier than the date upon which the name of each inventor is supplied unless a petition with the fee set forth in § 1.17(i) is filed which sets forth the reasons the delay in supplying the names should be excused. Administrative oversight is an acceptable reason. It should be noted that for a 35 U.S.C. 111(a) application to be entitled to claim the benefit of the filing date of a provisional application the 35 U.S.C. 111(a)[,] application must have at least one inventor in common with the provisional application." Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,209.*

*The term "invention" is typically used to refer to subject matter which applicant is claiming in his/her application. Because claims are not required in a provisional application, it would not be appropriate to reference joint inventors as those who have made a contribution to the "invention" disclosed in the provisional application. If the "invention" has not been determined in the provisional application because no claims have been presented, then the name(s) of those person(s) who have made a contribution to the subject matter disclosed in the provisional application should be submitted. Section 1.45(c) states that "if multiple inventors are named in a provisional application, each named inventor must have made a contribution, individually or jointly, to the subject matter disclosed in the provisional application." All that § 1.45(c) requires is that if someone is named as an inventor, that person must have made a contribution to the subject matter disclosed in the provisional application. When applicant has determined what the invention is by the filing of the 35 U.S.C. 111(a) application, that is the time when the correct inventors must be named. The 35 U.S.C. 111(a) application must have an inventor in common with the provisional application in order for the 35 U.S.C. 111(a) application to be entitled to claim the benefit of the provisional application under 35 U.S.C. 119(e). Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,208.*
*See 37 C.F.R. § 1.53.*

1. Peter — GIVEN NAME | C. — MIDDLE INITIAL OR NAME | MELTZER — FAMILY (OR LAST) NAME

2. Bertha — GIVEN NAME | Kalifon — MIDDLE INITIAL OR NAME | MADRAS — FAMILY (OR LAST) NAME

3. Residence address(es) of the inventor(s), as numbered above (37 C.F.R. § 1.51(c)(1)(iii)):

   1. **240 Salem Street, Woburn, Massachusetts 01801, USA**

   2. **1 Pine Hill Drive, Southborough, Massachusetts 01772, USA**

4. The title of the invention is (37 C.F.R. § 1.51(c)(1)(iv)):

   **PYROVALERONE ANALOGUES AND THERAPEUTIC USES THEREOF**

5. The name, registration, customer and telephone numbers of the practitioner *(if applicable)* are (37 C.F.R. § 1.51(c)(1)(v)):

   Name of practitioner: George W. Neuner

   Reg. No. 26,964 Tel. (617) 439-4444

   Customer No. 21874

   *(complete the following, if applicable)*

   [ ] A power of attorney accompanies this cover sheet.

6. The docket number used to identify this application is (37 C.F.R. § 1.51(c)(1)(vi)):

   Docket No. **59752-P (70207)**

7. The correspondence address for this application is (37 C.F.R. § 1.51(c)(1)(vii)):

   **EDWARDS & ANGELL, LLP, P.O. BOX 9169, Boston, Massachusetts 02209**

8. Statement as to whether invention was made by an agency of the U.S. Government or under contract with an agency of the U.S. Government. (37 C.F.R. § 1.51(c)(1)(viii)).

This invention was made by an agency of the United States Government, or under contract with an agency of the United States Government.

[X] No
[ ] Yes

The name of the U.S. Government agency and the Government Grant Number are:

**9.** Identification of documents accompanying this cover sheet:

**A.** Documents required by 37 C.F.R. §§ 1.51(c)(2)-(3):

| | | |
|---|---|---|
| Specification: | No. of pages: | 50 |
| Drawings: | No. of sheets: | 2 |

**B.** Additional documents:

*Note:* *See 37 C.F.R. § 1.51.*

[ ] Power of attorney
[ ] Assignment

*NOTE:* *Provisional applications may be filed in a language other than English as set forth in existing § 1.52(d). However, an English language translation is necessary for security screening purposes. Therefore, the PTO will require the English language translation and payment of the fee mandated in § 1.52(d) in the provisional application. Failure to timely submit the translation in response to a PTO requirement will result in the abandonment of the provisional application. If a 35 U.S.C. 111(a) application is filed without providing the English language translation in the provisional application, the English language translation will be required to be supplied in every 35 U.S.C. 111(a) application claiming priority of the non-English language provisional application. Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,209.*

**10.** Fee

The filing fee for this provisional application, as set in 37 C.F.R. § 1.16(k), is $160.00, for other than a small entity, and $80.00, for a small entity.

**[X] Applicant is a small entity.**
[ ] Applicant is not a small entity.

*NOTE:* *"A . . . statement in compliance with existing § 1.27 is required to be filed in each provisional application in which it is desired to pay reduced fees." Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,197.*

**11.** Small entity statement

[X] Applicant's state that this is a filing by a small entity under 37 C.F.R. §§ 1.9 and 1.27.

12. Fee payment

[X] Fee payment in the amount of **$80.00**.

[ ] No filing fee is to be paid at this time. (This and the surcharge required by 37 C.F.R. § 1.16(l) can be paid subsequently.)

13. Method of fee payment

[X] Check in the amount of **$80.00**.
[ ] Charge Account No. __________, in the amount of $ __________.
A duplicate of this Cover Sheet is attached.

Please charge Account No. 04-1105 for any fee deficiency.

Date: October 8, 2003

George W. Neuner (Reg. No: 26,964)
EDWARDS & ANGELL, LLP
PO BOX 9169
Boston, MA 02209

Tel.: (617) 439-4444

BOS2_350735v1

Express Mail Label No. EL 343 732 845 US
Docket No. 59752-P (70207)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**
**NEW PROVISIONAL PATENT APPLICATION**

TITLE: **PYROVALERONE ANALOGUES AND THERAPEUTIC USES THEREOF**

INVENTOR: Peter C. **MELTZER** and Bertha Kalifon **MADRAS**

FILING DATE: October 8, 2003

ATTORNEY: George W. Neuner (Reg. No. 26,964)
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PROVISIONAL PATENT APPLICATION
ATTORNEY DOCKET NO: 59752 P

# PYROVALERONE ANALOGUES AND THERAPEUTIC USES THEREOF

## FIELD OF THE INVENTION

The present invention relates to novel tropane compounds that have an affinity for a monoamine transporter, e.g., the dopamine transporter (DAT), or norepinephrine transporter (NET). Such agents can be useful for the early diagnosis and treatment of diverse neurological and psychiatric conditions.

## BACKGROUND OF THE INVENTION

Monoamine transporters play a variety of roles, and compounds with affinity for the monoamine transporters have been proposed for therapy and/or diagnosis of medical indications that include (but are not limited to) attention deficit hyperactivity disorder (ADHD), Parkinson's disease, cocaine addiction, smoking cessation, weight reduction, obsessive-compulsive disorder, various forms of depression, traumatic brain injury, stroke, and narcolepsy. Examples of monoamine transporters include, e.g., the dopamine transporter (DAT), serotonin transporter (SERT) or norepinephrine transporter (NET).

Therapies for treating diseases and disorders related to monoamine transport are needed. For example, there is a need for protective agents for neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease as well as therapeutic agents for dopamine related dysfunction such as Attention Deficit Disorder. Compounds that inhibit monoamine reuptake in the mammalian system are sought to provide such therapies.

Other neuropsychiatric disorders, including Tourette's Syndrome and Lesch Nyhan Syndrome and possibly Rett's syndrome, are also marked by changes in DAT density. The DAT also is the target of the most widely used drug for attention deficit disorder, methylphenidate. The capacity to monitor the transporter in persons suffering from this disorder can have diagnostic and therapeutic implications.

The density of the DAT in the brains of substance abusers has also been shown to deviate from that in normal brain. For example, the density is elevated in post-mortem tissues of cocaine

abusers (Little et al., Brain Res. 1993, 628, 17-25). On the other hand, the density of the DAT in chronic nonviolent alcohol abusers is decreased markedly. (Tiihonen et al., *Nature Medicine* 1995, 1, 654-657). Brain imaging of substance abusers can be useful for understanding the pathological processes of cocaine and alcohol abuse and monitoring restoration of normal brain function during treatment.

Accordingly, compounds that bind to the DAT provide important clinical information to assist in the diagnosis and treatment of these and other DAT related disease states. Serotonin (5-hydroxytryptamine) neurotransmission is regulated and terminated by active transport via the serotonin transporter (SERT). Inhibition of 5-hydroxytryptamine reuptake has an effect on diseases mediated by 5HT receptors. Compounds that provide such inhibition can be useful, for example, as therapeutic anti-depressants. Structurally related to dopamine and norepinephrine transporters (Nelson N. 1998. *J Neurochem* 71:1785-1803), the SERT is the primary site of action of diverse antidepressant drugs, ranging from tricyclics such as imipramine and amitriptyline, to serotonin selective reuptake inhibitors (SSRI's) such as citalopram, fluoxetine and sertraline.

Antidepressant drugs delay the removal of extracellular serotonin from the synapse by blocking serotonin transport, thereby prolonging the duration of serotonin receptor activity. The increased availability of serotonin triggers a cascade of neuroadaptive processes, which produces symptom relief after two to four weeks. Presently known antidepressants also produce certain side effects and may selectively alleviate specific symptoms of depression (Nestler EJ. 1998. *Biol Psychiatry* 44:526-533). Thus, it is desirable to develop novel antidepressants. The majority of clinically approved drugs to treat depression or obsessive-compulsive disorder are high affinity inhibitors of serotonin and/or norepinephrine transport. Of these transporter inhibitors, none are tropane analogs.

Norepinephrine regulates mood, is involved in learning and memory, and controls endocrine and autonomic functions. Dysfunction of norepinephrine neurotransmission has been implicated in depression, cardiovascular and thermal pathophysiology. The norepinephrine transporter (NET) regulates extracellular levels of norepinephrine in brain, in heart, and in the sympathetic nervous system. Clinically, the norepinephrine transporter is a principal target of selective or non-selective anti-depressant drugs and stimulant drugs of abuse such as cocaine and amphetamines. Blockade of the norepinephrine transporter is implicated in appetite suppression.

Gehlert et al. *J. Pharmacol. Exp. Ther.* 287:122-127 (1998). Imaging of the norepinephrine transporter may also be useful for viewing the status of sympathetic innervation in the heart and in other adrenergic terminals, and for detecting neuroblastomas. Hadrich et al. *J. Med. Chem.* 42:3010-3018 (1999); Raffel et al., *J. Nucl. Med.* 40:323-330 (1999).

Monoamine transporters such as, the dopamine transporter, serotonin transporter and norepinephrine transporter, are localized on monoamine nerve terminals. Compounds that bind to these sites can be useful as (i) probes for neuro-degenerative diseases (e.g., Parkinson's disease), (ii) therapeutic drugs for neurodegenerative diseases (e.g., Parkinson's and Alzheimer's disease), (iii) therapeutic drugs for dopamine dysfunction (e.g., Attention Deficit Disorder), (iv) treatment of psychiatric dysfunction (e.g., depression) and (v) treatment of clinical dysfunction (e.g., migraine).

It is desirable to avoid unwanted side effects of treatments targeting monoamine transporters, to the extent possible. It is also desirable to produce efficient and effective diagnostics for various conditions involving monoamine transporters.

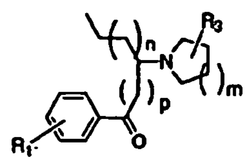
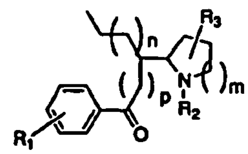
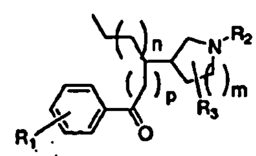
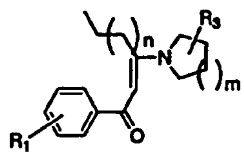
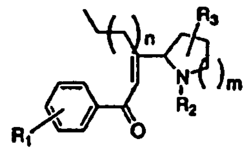
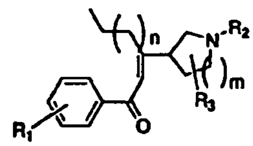
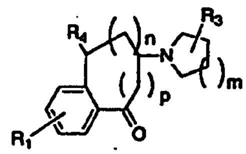
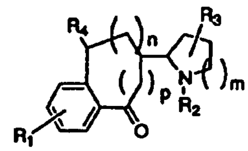
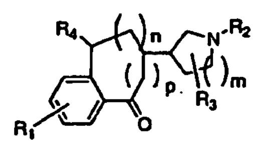
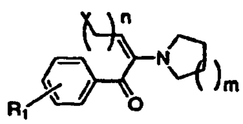
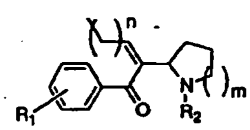
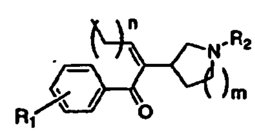
Furthermore, it would be useful to improve the bioavailability of compounds used to treat and/or diagnose monoamine transporter related diseases and disorders. It would be useful to modify these compounds to block or reduce metabolism of the compounds, while maintaining, or ideally, improving potency and/or selectivity of the compounds.

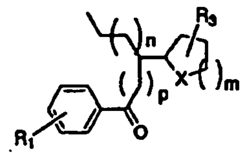
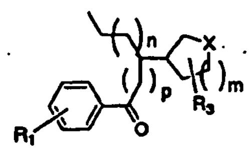
## SUMMARY OF THE INVENTION

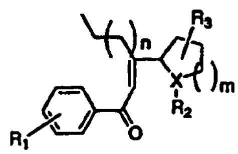
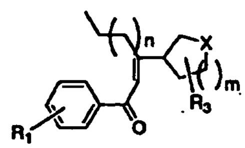
The present invention relates to compounds that bind and/or inhibit monoamine transporters such as the dopamine, serotonin and norepinephrine transporters of mammalian systems.

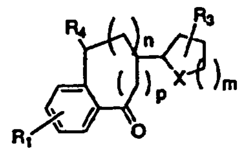
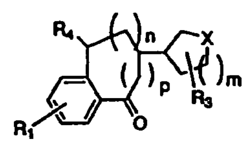
More specifically, the invention relates to tropane analogs, such as Pyrovalerone, that are active enantiomers of monoamine uptake systems and are selective for different monoamine uptake systems such as DAT, NET, and SERT. For example, an enantiomer 2S-pyrovalone (see Scheme I) is potent at DAT, ($IC_{50}$ = 3nM) and selective at SERT ($IC_{50}$ > 4 μM).

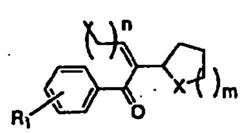
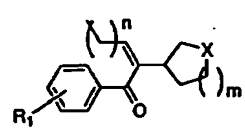
Compounds of the invention are represented by the following general formulae:

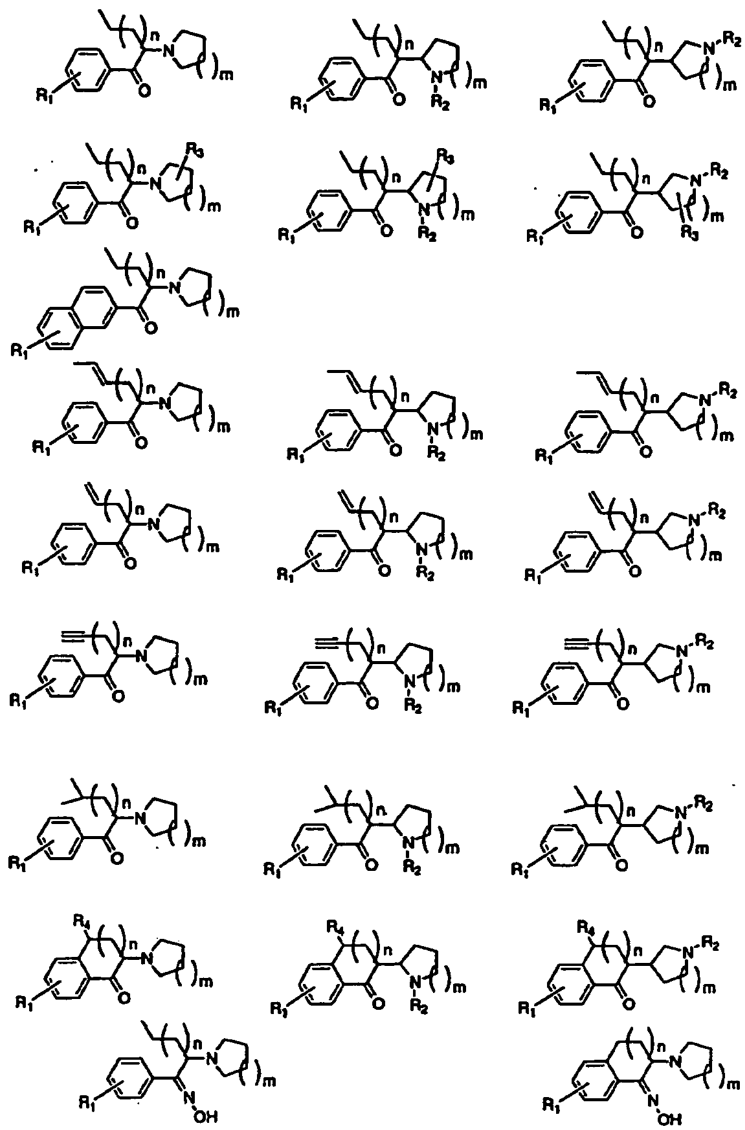











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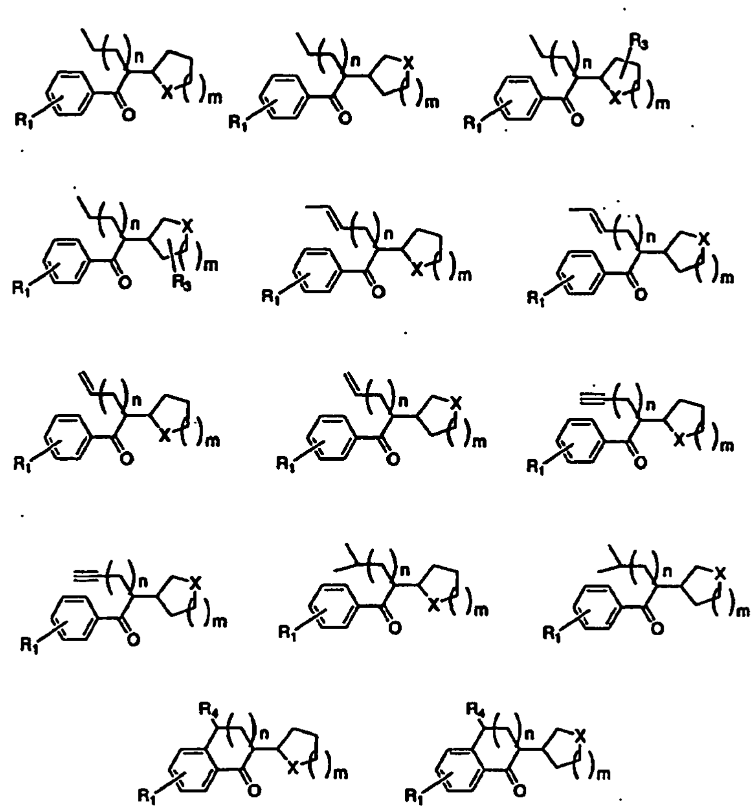


wherein,

$R_1$ = H; Br; Cl; I; F; OH; $OCH_3$; $CF_3$; $NO_2$; $NH_2$; CN; $NHCOCH_3$; $C(CH_3)_3$; $C(CH_2)CH_3$; $(CH_2)_qCH_3$ where q=0-6; $COCH_3$; alkyl; alkenyl; alkynyl; allyl; isopropyl; isobutyl; F (at the 2, 3 or 4 position); Cl (at the 2, 3 or 4 position); I (at the 2, 3 or 4 position) 3,4-diCl; 3-Cl,4-$C(CH_2)CH_3$; 3-Br,4-$C(CH_2)CH_3$; 3-I,4-$C(CH_2)CH_3$; 4-Cl,3-$C(CH_2)CH_3$; 4-Br,3-$C(CH_2)CH_3$; 4-I,3-$C(CH_2)CH_3$; 3,4-diOH; 3,4-diOAc; 3,4-di$OCH_3$; 3-OH,4-Cl; 3-OH,4-

F; 3-C1,4-OH; 3-F,4-OH; $CH_2OH$; $CH_2OCH_3$; $CH_2000CH_3$; $CH_2OR_2$; $(CH_2)_{„}000R_2$; $(CH_2)_nOR_2$;$(CH_2)_nOCOR_2$

$R_2$ = alkyl; alkenyl; alkynyl; allyl; isopropyl; isobutyl; H; $CH_3$; $CH_2ArR_1$; $(CH_2)_{n,}$Ar(phenyl or naphthyl)$R_1$

$R_3$ = alkyl; alkenyl; alkynyl; allyl; isopropyl; isobutyl; H; $CH_3$; $CH_2ArR_1$; $(CH_2)_nArR_1$; H; Br; Cl; I; F; OH; $OCH_3$; $CF_3$; $NO_2$; $NH_2$; CN; $NHCOCH_3$; $C(CH_3)_3$; $C(CH_2)CH_3$; $(CH_2)qCH_3$ where q=0-6; $COCH_3$; $CH_2OH$; $CH_2OCH_3$; $CH_2OCOCH_3$; $CH_2OR_2$; $(CH_2)_nOCOR_2$; $(CH_2).OR_2$; $(CH_2)_n$ $OCOR_2$

n = 0 - 4

m, p = 0 - 2

X = O, $CH_2$, S, $SO_2$, SO

The compounds of the present invention can be racemic or pure S-enantiomers. Thus, the structural formulae illustrated herein are intended to represent each enantiomer and diastereomer of the illustrated compound.

The compounds of the present invention can be radiolabeled, for example, to assay cocaine receptors. Certain preferred compounds of the present invention have a high selectivity for the DAT versus the SERT. Preferred compounds have an $IC_{50}$ SERT/DAT ratio of greater than about 10, preferably greater than about 30 and more preferably 50 or more. In addition, preferably the compounds have an $IC_{50}$ at the DAT of less than about 500 nM, preferably less than 60 nM, more preferably less than about 20 nM and most preferably less than about 3 nM.

The present invention also provides pharmaceutical therapeutic compositions comprising the compounds formulated in a pharmaceutically acceptable carrier.

Preferred monoamine transporters for the practice of the present invention include the dopamine transporter, the serotonin transporter and the norepinephrine transporter.

In a preferred embodiment, the invention also provides a method for inhibiting dopamine reuptake of a dopamine transporter by contacting the dopamine transporter with a dopamine reuptake inhibiting amount of a compound of the present invention. Inhibition of dopamine reuptake of a dopamine transporter in a mammal is provided in accord with the present invention by administering to the mammal a dopamine inhibiting amount of a compound of the present invention in a pharmaceutically acceptable carrier. Figure 1 is illustrative of the compounds of

the present invention such as Pyrovalerone, that are active enantiomers of monoamine uptake systems and are selective for different monoamine uptake systems such as DAT, NET, and SERT. For example, an enantiomer 2S-pyrovalone (see Scheme I) is potent at DAT, ($IC_{50}$ = 3nM) and selective at SERT ($IC_{50} > 4$ μM).

The invention also relates to a method for treating a mammal having a disorder selected from neurodegenerative disease, psychiatric dysfunction, dopamine dysfunction, cocaine abuse and clinical dysfunction comprising administering to the mammal an effective amount of a compound of the present invention. In certain methods, the neurodegenerative disease is selected from Parkinson's disease and Alzheimer's disease. An example of a psychiatric disorder which can be treated by the present methods is depression.

The invention also relates to methods for treating dopamine related dysfunction in a mammal comprising administering to the mammal a dopamine reuptake inhibiting amount of a compound as described herein. An example of a dopamine related dysfunction is Attention deficit disorder.

The invention also relates to methods for treating serotonin related dysfunction in a mammal comprising administering to the mammal a serotonin reuptake inhibiting amount of a compound as described herein.

The invention also relates to methods for treating norepinephrine related dysfunction in a mammal comprising administering to the mammal a norepinephrine reuptake inhibiting amount of a compound as described herein.

The term "lower alkyl" when used herein designates aliphatic saturated branched or straight chain hydrocarbon monovalent substituents containing from 1 to about 8 carbon atoms such as methyl, ethyl, isopropyl, n-propyl, n-butyl, (CH2)nCH3, C(CH3)3; etc., more preferably 1 to 4 carbons. The term "lower alkoxy" designates lower alkoxy substituents containing from 1 to about 8 carbon atoms such as methoxy, ethoxy, isopropoxy, etc., more preferably 1 to 4 carbon atoms.

The term "lower alkenyl" when used herein designates aliphatic unsaturated branched or straight chain vinyl hydrocarbon substituents containing from 2 to about 8 carbon atoms such as allyl, etc., more preferably 2 to 4 carbons. The term "lower alkynyl" designates lower alkynyl substituents containing from 2 to about 8 carbon atoms, more preferably 2 to 4 carbon atoms such as, for example, propyne, butyne, etc.

The terms substituted lower alkyl, substituted lower alkoxy, substituted lower alkenyl and substituted lower alkynyl, when used herein, include corresponding alkyl, alkoxy, alkenyl or alkynyl groups substituted with halide, hydroxy, carboxylic acid, or carboxamide groups, etc. such as, for example, -CH2OH, -CH2CH2COOH, -CH2CONH2, -OCH2CH2OH, -OCH2COOH, -OCH2CH2CONH2, etc. As used herein, the terms lower alkyl, lower alkoxy, lower alkenyl and lower alkynyl are meant to include where practical substituted such groups as described above.

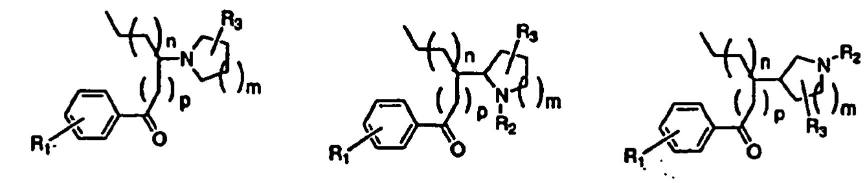
When X contains a carbon atom as the ring member, reference to X is sometimes made herein as a carbon group. Thus, when X is a carbon group, as that phrase is used herein, it means that a carbon atom is a ring member at the X position.

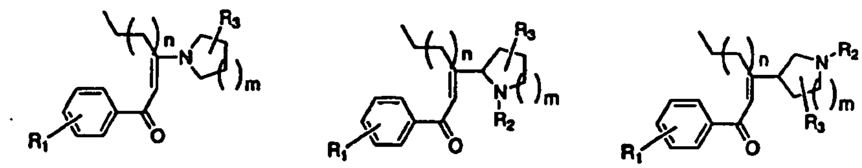
BRIEF DESCRIPTION OF THE FIGURES

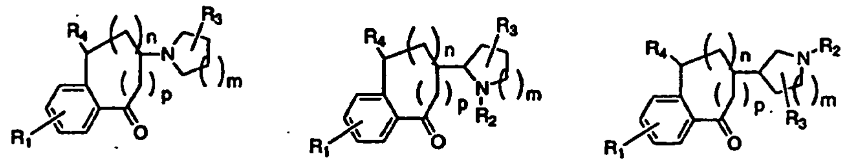
Figure 1 is a chart showing the compounds of the invention and their $K_i$ with respect to DAT, SERT and NET.

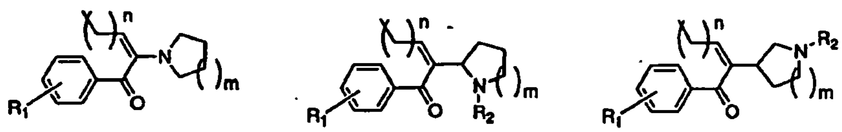
DETAILED DESCRIPTION OF THE INVENTION

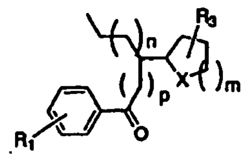
In accord with the present invention, novel tropane compounds are provided that bind to monoamine transporters, preferably the DAT. Certain preferred compounds also have a high selectivity for the DAT versus the SERT. Preferred compounds of the invention include those having the formula:

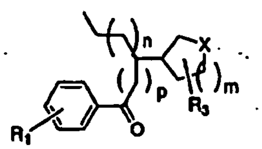


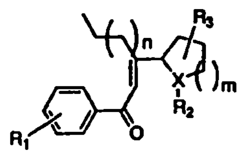


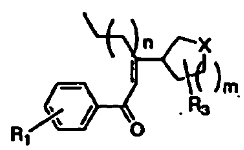


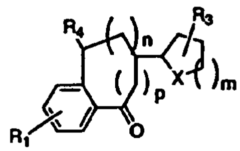


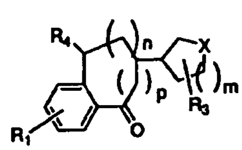


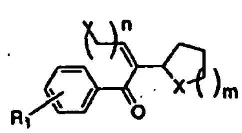


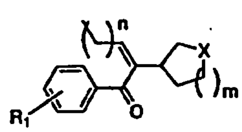


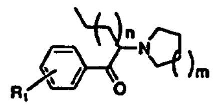
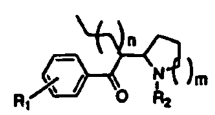
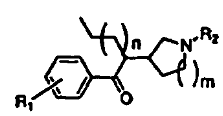


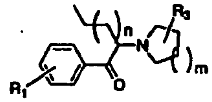
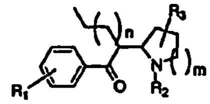
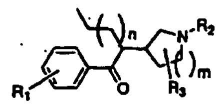


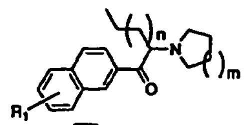


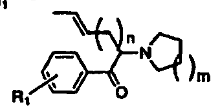
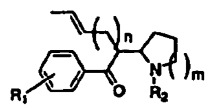
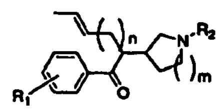


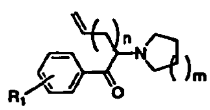
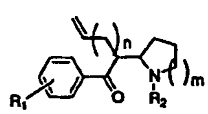
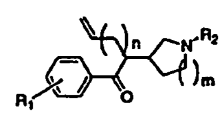


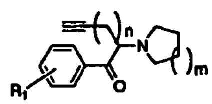
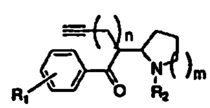
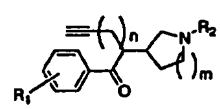
  

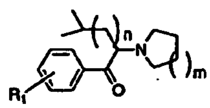
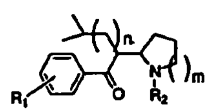
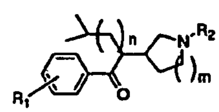
  

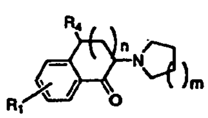
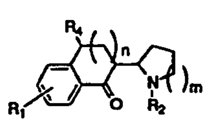
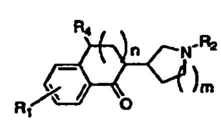


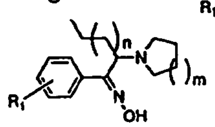
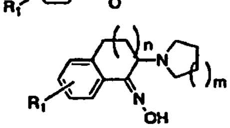
  

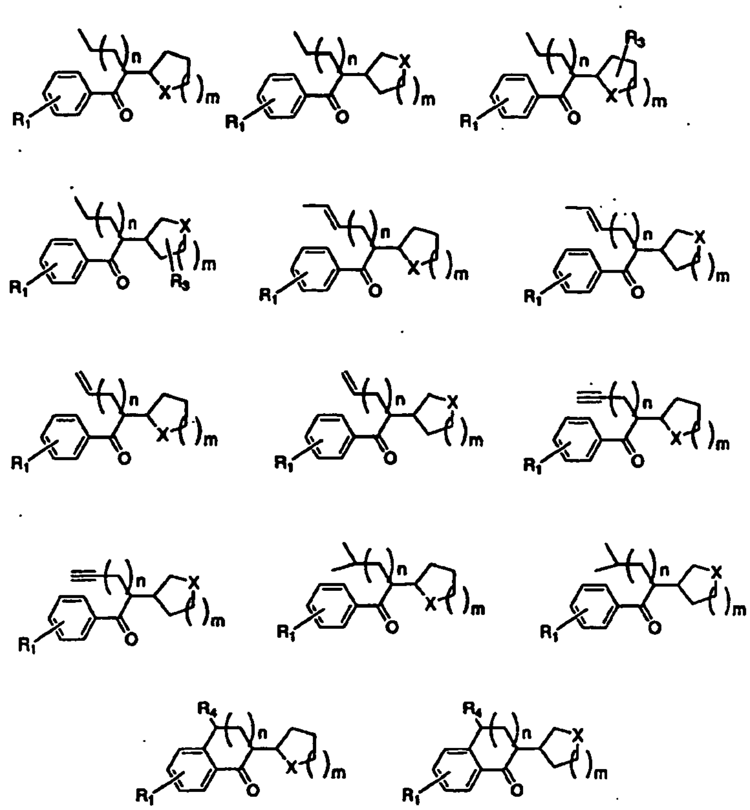
  



wherein,

$R_1$ = H; Br; Cl; I; F; OH; $OCH_3$; $CF_3$; $NO_2$; $NH_2$; CN; $NHCOCH_3$; $C(CH_3)_3$; $C(CH_2)CH_3$; $(CH_2)_qCH_3$ where q=0-6; $COCH_3$; alkyl; alkenyl; alkynyl; allyl; isopropyl; isobutyl; F (at the 2, 3 or 4 position); Cl (at the 2, 3 or 4 position); I (at the 2, 3 or 4 position) 3,4-diCl; 3-C1,4-$C(CH_2)CH_3$; 3-Br,4-$C(CH_2)CH_3$; 3-I,4-$C(CH_2)CH_3$; 4-C1,3-$C(CH_2)CH_3$; 4-Br,3-$C(CH_2)CH_3$; 4-I,3-$C(CH_2)CH_3$; 3,4-diOH; 3,4-diOAc; 3,4-di$OCH_3$; 3-OH,4-Cl; 3-OH,4-

F; 3-C1,4-OH; 3-F,4-OH; $CH_2OH$; $CH_2OCH_3$; $CH_2000CH_3$; $CH_2OR_2$; $(CH_2)_{,,}000R_2$; $(CH_2)_nOR_2$;$(CH_2)_nOCOR_2$

$R_2$ = alkyl; alkenyl; alkynyl; allyl; isopropyl; isobutyl; H; $CH_3$; $CH_2ArR_1$; $(CH_2)_{n,}$Ar(phenyl or naphthyl)$R_1$

$R_3$ = alkyl; alkenyl; alkynyl; allyl; isopropyl; isobutyl; H; $CH_3$; $CH_2ArR_1$; $(CH_2)_nArR_1$; H; Br; Cl; I; F; OH; $OCH_3$; $CF_3$; $NO_2$; $NH_{2;}$ CN; $NHCOCH_3$; $C(CH_3)_3$; $C(CH_2)CH_3$; $(CH_2)qCH_3$ where q=0-6; $COCH_3$; $CH_2OH$; $CH_2OCH_3$; $CH_2OCOCH_3$; $CH_2OR_2$; $(CH_2)_nOCOR_2$; $(CH_2).OR_2$; $(CH_2)_n$ $OCOR_2$

n = 0 - 4

m, p = 0 - 2

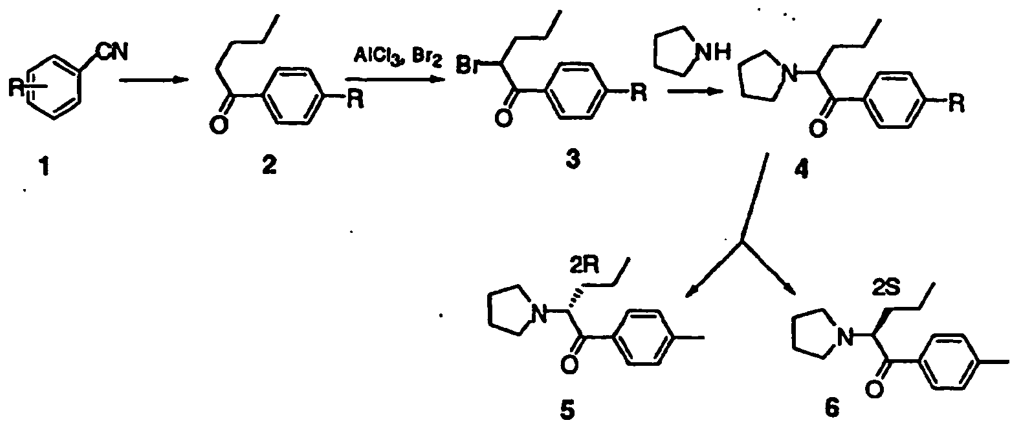
X = O, $CH_2$, S, $SO_2$, SO

In accord with the present invention, novel tropane compounds are provided that bind to monoamine transporters, preferably the DAT. Certain preferred compounds also have a high selectivity for the DAT versus the SERT.

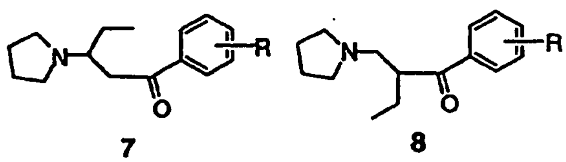
In a preferred embodiment, the novel tropane compounds, for example pyrovalerone analogs are potent and selective DAT inhibitors (Table 1).

Synthesis of these analogs is easily achieved as explained in detail in the examples which follow and exemplified as shown in Scheme I. An energy minimization and overlay was conducted of WIN 35,428 and the 2R and 2S enantiomers of pyrovalerone wherein the pyrrolidine nitrogens and the centroids of the aromatic rings were used as overlay controls. The propyl side chain in the 2S-configuration clearly overlays with the C2-β-carbomethoxy of the tropane. However the 2R-pyrovalerone overlay places the propyl chain in a position similar to that of the 2α-carbomethoxy of the tropane (azabicyclo[3.2.l]octane).

The starting materials, **2**, are commercially available or accessible by literature routes from 1 (a substituted benzonitrile) or valerophenone. Bromination ($Br_2$, $AlCl_3$) of **2** proceeds quantitatively and treatment with the secondary amine provides 4 in good yield. Other analogs have alternate aromatic systems, e.g. naphthyl, thiophene or pyrrole, shorter or longer alkyl chains, or are compounds in which the N to aromatic centroid distance has been altered (e.g. **7**, **8**).




| R | R | R |
|---|---|---|
| a. 4-$CH_3$ | h. 3-$CH_3$ | m. 4-OH |
| b. H | i. 3-F | n. 4-$OCH_3$ |
| c. 4-F | j. 3-Br | o. 4-$NH_2$ |
| d. 4-Br | k. 3-Cl | p. 4-$NHCOCH_3$ |
| e. 4-Cl | l. 3-I | q. 4-$NO_2$ |
| f. 3,4-$Cl_2$ | | r. 4-$CF_3$ |
| g. 4-I | | |




SCHEME I

The compounds of the present invention provide a broad array of molecules including compounds that bind with very high affinity. Selectivity for inhibition of the DAT versus the serotonin transporter (SERT) is another property of tropanes of considerable relevance for development of medications and for probes useful to image the DAT in living brain. Preferred compounds for DAT imaging agents have high DAT:SERT selectivity.

The compounds of the present invention can exhibit extremely potent and selective binding for the DAT. Preferred compounds of the present invention exhibit the desired target:non-target (DAT:SET) specificity. Preferably, the selectivity ratio of binding of SERT to binding of DAT is greater than about 10, preferably greater than about 30 and more preferably

50 or more.

In addition, the compounds are potent, having an $IC_{50}$ less than about 500 nM, preferably less than 60 nM, more preferably less than about 20 nM, and most preferably less than about 3 nM.

Using the combination of selectivity (SERT/DAT ratio) and potency ($IC_{50}$) information for these compounds, one of ordinary skill in the art can readily select the appropriate compound for the desired application, e.g., imaging or treatment. The DAT is enantioselective (Reith, M. E. A. et al., *Biochem. Pharmacol.* 1986, *35*, 1123-1129; Ritz, M. C. et al., *Science* 1987, *237*, 1219-1223; Madras, B. K. et al., *J. Pharmacol. Exp. Ther.* 1989, *251*, 131-141; Meltzer, P. C. et al., *J. Med. Chem.* 1994, *37*, 2001-2010; Sershen, H. et al., *Neuropharmacology* 1980, *19*, 1145-1148; Carroll, F. I. et al., *J. Med. Chem.* 1992, *35*, 969-981; Carroll, F. I. et al., in *Drug Design for Neuroscience*; A. P. Kozikowski, Ed.; Raven Press, Ltd. New York, 1993; 149-166).

The compounds of the invention can be prepared either as free bases or as a pharmacologically active salt thereof such as hydrochloride, tartrate, sulfate, naphthalene-1,5-disulfonate or the like.

The present invention also provides pharmaceutical compositions, preferably comprising the compounds of the present invention in a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known to those skilled in the art. An exemplary pharmaceutical composition is a therapeutically effective amount of a compound of the invention optionally included in a pharmaceutically-acceptable and compatible carrier. The term "pharmaceutically-acceptable and compatible carrier" as used herein, and described more fully below, refers to e.g., one or more compatible solid or liquid filler diluents or encapsulating substances that are suitable for administration to a human or other animal. The route of administration can be varied but is principally selected from intravenous, nasal and oral routes. For parenteral administration, e.g., it will typically be injected in a sterile aqueous or non-aqueous solution, suspension or emulsion in association with a pharmaceutically-acceptable parenteral carrier such as physiological saline.

The term "therapeutically-effective amount" is that amount of the present pharmaceutical compositions which produces a desired result or exerts a desired influence on the particular condition being treated. Various concentrations may be used in preparing compositions incorporating the same ingredient to provide for variations in the age of the patient to be treated,

the severity of the condition, the duration of the treatment and the mode of administration. An effective dose of the compound is administered to a patient based on $IC_{50}$ values determined in vitro.

The term "compatible", as used herein, means that the components of the pharmaceutical compositions are capable of being commingled with the compounds of the present invention, and with each other, in a manner such that there is no interaction that would substantially impair the desired pharmaceutical efficacy.

Dose of the pharmaceutical compositions of the invention will vary depending on the subject and upon particular route of administration used. Pharmaceutical compositions of the present invention can also be administered to a subject according to a variety well-characterized protocols.

In a preferred embodiment, the pharmaceutical composition is a liquid composition in pyrogen-free, sterilized container or vial. The container can be unit dose or multidose.

The compounds and pharmaceutical preparations of the present invention can be used to inhibit the %-hydroxytryptamine reuptake of a monoamine transporter, particularly reuptake by the dopamine transporter, serotonin transporter or norepinephrine transporter.

Dysfunction of dopamine neurons has been implicated in several neuropsychiatric diseases. Imaging of the dopamine neurons offers important clinical information relevant to diagnosis and therapeutic treatments. Dopamine neurons produce dopamine, release the neurotransmitter and remove the released dopamine with a dopamine transporter protein. Compounds that bind to the dopamine transporter are effective measures of dopamine neurons and can be transformed into imaging agents for PET and for SPECT imaging. In identifying a suitable compound for the dopamine transporter, an essential first step is to measure the affinity and selectivity of a candidate at the dopamine transporter. The affinity is measured by conducting radioreceptor assays. A radiolabeled marker for the transporter, e.g., ($^3$H)WIN 35,428, is incubated with the unlabeled candidate and a source of the transporter, usually brain striatum. The effect of various concentrations of the candidate on inhibiting ($^3$H)WIN 35,428 binding is quantified. The concentration of the compound that inhibits 50% of ($^3$H)WIN 35,428 bound to the transporter ($IC_{50}$ value) is used as a measure of its affinity for the transporter. A suitable range of concentrations of the candidate typically is about 1nM up to about 10 nM.

It is also important to measure the selectivity of the candidate of the dopamine compared

with the serotonin transporter. The serotonin transporter is also detectable in the striatum, the brain region with the highest density of dopamine neurons and in brain regions surrounding the striatum. It is necessary to determine whether the candidate compound is more potent at the dopamine than the serotonin transporter. If more selective (>10-fold), the probe will permit accurate measures of the dopamine transporter in this region of interest or will provide effective treatment modality for the dopamine transporter. Therefore, a measure of probe affinity of the serotonin transport is conducted by assays paralleling the dopamine transporter assays. ($^3$H)Citalopram is used to radiolabel binding sites on the serotonin transporter and competition studies are conducted with the candidate compound at various concentrations in order to generate an $IC_{50}$ value.

This invention will be illustrated further by the following examples. These examples are not intended to limit the scope of the claimed invention in any manner. The Examples provide suitable methods for preparing compounds of the present invention. However, those skilled in the art may make compounds of the present invention by any other suitable means. As is well known to those skilled in the art, other substituents can be provided for the illustrated compounds by suitable modification of the reactants.

All exemplified target compounds are fully analyzed (mp, TLC, CHN, GC and/or HPLC) and characterized ($^1$H NMR, $^{13}$C NMR, MS, IR) prior to submission for biological evaluation. The affinity of all the compounds for the DAT, SERT and NET are measured. NMR spectra are recorded on a Bruker 100, a Varian XL 400, or a Bruker 300 NMR spectrometer. Tetramethylsilane ("TMS") is used as internal standard. Melting points are uncorrected and are measured on a Gallenkamp melting point apparatus. Thin layer chromatography (TLC) is carried out on Baker Si 250F plates. Visualization is accomplished with iodine vapor, UV exposure or treatment with phosphomolybdic acid (PMA). Preparative TLC is carried out on Analtech uniplates Silica Gel GF 2000 microns. Flash chromatography is carried out on Baker Silica Gel 40mM. Elemental Analyses are performed by Atlantic Microlab, Atlanta, GA and are within 0.4% of calculated values for each element. A Beckman 1801 Scintillation Counter is used for scintillation spectrometry. 0.1% Bovine Serum Albumin ("BSA") is purchased from Sigma Chemicals. All reactions are conducted under an inert ($N_2$) atmosphere.

$^3$H-WIN 35,428 ($^3$H-CFT, 2β-carbomethoxy-3β-(4-fluorophenyl)-N-$^3$H-methyltropane, 79.4-87.0 Ci/mmol) and $^3$H-citalopram (86.8 Ci/mmol) is purchased from DuPont-New England

Nuclear (Boston, MA). HPLC analyses are carried out on a Waters 510 system with detection at 254 nm on a Chiralcel OC column (flow rate: 1 mL/min).

**TABLE 1**

| | | | CALCULATED | | | | | FOUND | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| COMPOUND # | ORGANIX # | CALCULATED FOR FORMULA | C | H | N | Cl | | C | H | N | Cl |
| db-236-7 | 0.2558 | C17H24CIN03 | 62.67 | 7.42 | 4.30 | 10 88 | | 62.45 | 7.59 | 4.31 | 10.78 |
| db-221-194 | 0.2555 | C23H32CINO | 73.87 | 8.63 | 3.75 | 9.48 | | 73.70 | 8.57 | 3.71 | 9.78 |
| db-221-202 | 0-2556 | C16H22CINO | 68.68 | 7.93 | 5.01 | 12.67 | | 68.64 | 7.97 | 5.02 | 12.50 |
| db-221-208 | 0-2557 | C15H15C13NO | 53.83 | 542 | 4.19 | 31.78 | | 53.82 | 5.55 | 4.07 | 31.65 |
| db-221-182 | 0-2574 | C15H22BrNO3 | 52.34 | 6.44 | 4.07 | 23.21(Br | | 52.40 | 6.48 | 4.03 | 22.98 |
| db-236-3 | 0-2575 | C16H21CIN20.1/4H2O | 64.64 | 7.29 | 9.42 | 11.92 | | 64.74 | 729 | 9.31 | 11.92 |
| db-236-33 | 0-2576-1 | C16H2OCINO | 69.18 | 7.26 | 5.04 | 12.76 | | 68.91 | 7.36 | 5.05 | 12.97 |
| db-236-20 | 0-2577 | C16H24CIN02.1/4H2O | 63.57 | 8.17 | 4.63 | 11 73 | | 63.55 | 8.13 | 4.68 | 11.55 |
| db-221-165-1 | 0-2536 | C17H25BRCIN03.2/3H2O | 48.76 | 6.34 | 3.34 | 8.47 | | 48.65 | 6.28 | 3.33 | 8.44 |
| db-221-179-1 | 0-2529 | C16H226CINO | 67.71 | 9.23 | 4.93 | 12.49 | | 67.70 | 9.26 | 4.91 | 12.55 |
| db-221-181 | 0-2537 | C18H24CINO | 70.69 | 7.91 | 4.58 | 11.59 | | 70.45 | 7 96 | 4.59 | 11.81 |
| db-221-167 | 0-2512 | C17H26CIN03 | 62.28 | 7.99 | 4.27 | 10.81 | | 62.04 | 8.01 | 4.24 | 11.06 |
| db-221-149 | 0-2494 | C17H26CINO | 69.02 | 8 86 | 4.73 | 11.98 | | 68.92 | 8.84 | 4.69 | 12.00 |
| db-221-148 | 0-2493 | C15H21C11NO | 45.76 | 5.38 | 3.56 | 9.01 | | 45.81 | 5.49 | 3.59 | 9.17 |
| db-221-140 | 0-2482 | C19H24CINO | 71.80 | 7.61 | 4.41 | 11.15 | | 71.53 | 7.72 | 4.41 | 11.14 |
| db-221-136 | 0-2481 | C16H21CIF3NO | 57.23 | 6.30 | 4.17 | 10.56 | | 57.12 | 634 | 4.14 | 10.44 |
| db-221-135 | 0-2480 | C16H24CINO | 68.19 | 8.58 | 4.97 | 12.58 | | 68.07 | 8.68 | 4.88 | 12.67 |
| db-221-134 | 0-2479 | C16H24CIN0.92/100H2O | 64.42 | 8.73 | 4.69 | 11.88 | | 64.39 | 8.69 | 4.71 | 11.98 |
| db-221-121 | 0-2477 | C17H26CINO | 69.02 | 8.86 | 4.73 | 11.98 | | 68.95 | 8.94 | 4.77 | 12.09 |
| db-221-122-1 | 0-2478 | C16H22C13NO | 54.80 | 6.32 | 3.99 | 30.33 | | 54.82 | 636 | 4.06 | 30.39 |
| db-221-99 | 0-2446 | C20H27CIN20.2/3H2O | 66.93 | 7.96 | 7.81 | 9.88 | | 66.85 | 7.88 | 7.79 | 9.82 |
| db-221-93-1-2 | 0-2441 | C16H24CINO | 68.19 | 8.58 | 4.97 | 12.58 | | 68.06 | 8.60 | 4.96 | 12.47 |
| db-221.93-2 | 0-2442 | C16H24CINO | 68.19 | 8.58 | 4.97 | 12.58 | | 68.24 | 8.62 | 4.99 | 12.48 |
| db-221-92 | 0-2438 | C19H24CIN05 | 65.22 | 6.91 | 4.00 | 10.13 | | 65.11 | 6.77 | 3.96 | 9.99 |
| db-221-90 | 0-2441 | C19H24CIN02 | 68.36 | 7.25 | 4.20 | 10 62 | | 68.11 | 7.17 | 4.21 | 10.67 |
| db-221-89 | 0-2443 | C15H21C1N203.0.42H20.0.08HCI | 55.72 | 6.83 | 8.66 | 11.88 | | 55 73 | 6.80 | 8.48 | 11.91 |
| db-221-80 | 0-2439 | C17H25CIN202.1/2H2O | 61.16 | 7.85 | 8.39 | 10.62 | | 61.32 | 7.70 | 8.40 | 10.68 |
| db-221-72 | 0-2419 | C15H21BrCINO | 51.97 | 6.11 | 4.04 | 10.23 | | 51.78 | 6.00 | 3.95 | 10.28 |
| db-221 :68-3 | 0-2418 | C15H22CIN02 | 63.48 | 7.81 | 4.94 | 12.49 | | 63.43 | 7.90 | 5.00 | 12.30 |
| db-221-58 | 0-2417 | C16H24CIN02.1/2H20.1/2HCI | 59.12 | 7.91 | 4.31 | 16.36 | | 59.39 | 8.07 | 4.36 | 16.22 |
| db-221-179-2 | 0-2530 | C16H26CINO | 67.71 | 9.23 | 4.93 | 1249 | | 67.47 | 9.29 | 4.94 | 12.56 |
| db-221-190 | 0-2539 | C13H18CINO | 65.13 | 7.57 | 5.84 | 14.79 | | 65.30 | 7.62 | 5.83 | 14.85 |
| db-221-186 | 0-2538 | C12H14CI3NO | 48.92 | 4 79 | 4.75 | 36.10 | | 48.91 | 4 77 | 4.67 | 36 02 |
| db-221-151 | 0-2511 | C17H25CIN0.38/100H2O | 67.48 | 8.91 | 4.63 | 11 72 | | 67.40 | 892 | 4.61 | 11.54 |
| db-221-178 | 0-2525 | C16H24CINO | 68.19 | 8.58 | 4 97 | 12.58 | | 68.11 | 8.55 | 5.01 | 12.70 |
| db-221-177 | 0-2524 | C15H2OCI3NO.1/3H2O | 52.57 | 6.08 | 4.09 | 31.04 | | 52.40 | 5.98 | 4.18 | 31.28 |
| db-221-158 | 0-2495 | C15H21CIINO | 45.76 | 5.38 | 3.56 | 9.01 | | 45.65 | 5.37 | 3.5 | 8.88 |
| db-221-32 | 0-2390 | C15H2OCI3NO | 53.51 | 5.99 | 4.16 | 31.59 | | 53.37 | 5 93 | 4.14 | 31.65 |
| db-221-29-3 | 0-2389 | C15H22C13NO | 53.19 | 6.55 | 414 | 31.4 | | 5313 | 6.48 | 4.12 | 31.55 |
| db-221-28 | 0-2388 | C16H22C13NO | 54.80 | 6.32 | 3.99 | 30.33 | | 54.62 | 6.34 | 4.08 | 30 52 |
| db-221-26 | 0-2387 | C1 SH22CINO | 67.28 | 8.28 | 5 23 | 13.24 | | 67.50 | 8.35 | 5.18 | 13 12 |
| db-221-8 | 0-2370 | C15H21CIFNO | 63.04 | 7.41 | 4.90 | | | 63.32 | 745 | 4.85 | |
| db-221-18c | 0-2384 | C14H18CI3NO | 52.11 | 5.62 | 4.34 | | | 52.14 | 5.55 | 4.26 | |
| db-221-12 | 0-2371 | C16H24CINO.1/6H2O | 67.47 | 861 | 4.92 | | | 67.47 | 856 | 4.91 | |

EXAMPLES

*Materials and Methods*

Compounds were prepared employing the same method, General Procedure A as illustrated by Scheme I, except where noted. α-Bromoketone (10 mmol) was dissolved in $Et_2O$ (10 mL) (EtOH is a suitable alternative solvent) and cooled on an ice bath. Pyrrolidine (22

mmol) was added all at once. The mixture became orange and an oil was observed to separate from the solution. After 1 - 24 h stirring at room temperature, the crude reaction mixture was partitioned between $H_2O$ (10 mL) and $Et_2O$. The $Et_2O$ layer was separated and the aqueous layer was washed with $Et_2O$ (2 x 10 mL). The ether layer was extracted with I M aqueous HCI (2 x 10 mL), then back-extracted into $Et_20$ (3 x 10 mL) by basification to pH 8-9 with 20% aqueous $Na_2CO_3$. The $Et_2O$ extracts were dried ($MgSO_4$) and filtered. The filtrate was treated with 2 M ethereal HCI (usually 5 - 10 mL) until precipitation of solid or oil had ceased. Solids (oils were triturated to give solids) were collected by filtration and recrystallized from EtOH/$Et_2O$.

*Example 1*

**1-(3,4-Dihydroxy-phenyl)-2-pyrrolidin- 1 -yl-pentan- 1 -one, hydrogen bromide salt.** 1-(3,4-Dimethoxyphenyl)-2-pyrrolidin-1-yl-pentan-l-one (1.50 g, 4.6 mmol) was freed from its hydrogen chloride salt by treatment with aqueous $Na_2CO_3$ and extracting into $CH_2CI_2$. The organics were dried ($MgS0_4$), filtered, and reduced to a pale yellow oil *in vacuo.* The oil was taken up in $CH_2C1_2$ (10 mL) and cooled to -78 °C, whereon $BBr_3$ (46 mL, 1.0 M solution in $CH_2C1_2$, 46 mmol) was added dropwise over 0.5 h. The resulting yellow mixture was warmed slowly to room temperature and stirred for 3 h. The yellow solution was hydrolyzed cautiously by addition of aq. $Na_2CO_3$ (20% solution) until the pH was 8, then water (50 mL) was added and the solution was allowed to stand overnight. Neutral organics were extracted from the mixture by separation of the $CH_2C1_2$ layer which was then discarded. The aqueous layer was acidified to pH 3 with 1 M HCI, most of the water was removed by rotary evaporation, and the remaining volume of ca 10 mL was allowed to cool in the refrigerator. After 3 d, a white solid separated from the solution and was collected by filtration. Recrystallization (EtOH/$Et_2O$) afforded pure 1-(3,4-dihydroxyphenyl)-2-pyrrolidin-l-yl-pentan-l-one (0.60 g, 44%) as its hydrogen bromide salt, an off-white solid; Mp 181 - 182 °C; $^1$H NMR δ 10.42 (s, 1H), 10.1 - 9.9 (br, 1H), 9.59 (s, 1H), 7.51 (dd, I H), 7.43 (d, 1H), 6.91 (d, 111), 5.35 - 5.25 (br, 111), 3.75 - 3.5 (br, 1H). 3.5 - 3.3 (br, I H), 3.3 - 3.15 (br, 1H), 3.0 - 2.85 (br, 1H), 2.1 - 1.8 (m, 6H), 1.3 - 1.0 (m, 2H), 0.80 (t, $J$ = 7 Hz, 3H); $^{13}$C NMR δ 194.8, 153.4, 146.4, 126.7, 123.5, 116.0, 115.9, 675, 54.5, 52.3, 32.8, 23.2, 17.9, 14.3; APCI MS m/z 264 (M + 1); Anal. ($C_{15}H_{22}BrNO_3$) C, H, N, Br.

*Example 2*

**4-(2-Pyrrolidin-1-yl-pentanoyl)-benzonitrile, hydrogen chloride salt.** This compound was prepared, in 70% yield, as described in General Procedure A, with slight modifications; Mp

197 - 199 °C (dec.); $^1$H NMR δ 10.9 - 10.7 (br, 1H), 8.24 (d, 2H), 8.14 (d, 2H), 5.7 - 5.55 (br, m, 1H), 3.7 - 3.6 (br, m, 1H), 3.6 - 3.5 (br, m, 1 H), 3.3 - 3.1 (br, m, 2H), 2.1 - 1.8 (m, 6H), 1.4 - 1.2 (m, 1 H), 1.1 - 0.9 (m, 1 H), 0.77 (t, $J = 7$ Hz, 3H); $^{13}$C NMR δ 196.2, 137.5, 133.2, 129.4, 117.9, 116.6, 67.8, 53.7, 51.9, 31.3, 22.9, 17.2, 13.7; APCI MS *m/z* 257 (M + 1); Anal. ($C_{16}H_{21}ClN_2O.1/4H_2O$) C, H, N, Cl.

*Example 3*

**2-Pyrrolidin-1-yl-1 p-tolyl-pent-4-yn-1-one, hydrogen chloride salt.** 2-Pyrrolidin-l-yl-l-p-tolyl-ethanone, (25 g, 104 mmol) was freed from its hydrogen chloride salt by treatment with aqueous $Na_2CO_3$ and extraction into $Et_2O$. The organics were dried ($MgSO_4$), filtered and reduced *in vacuo* to a yellow oil. This oil was taken up in toluene (200 mL), and $NaNH_2$ was added to the stirring solution which was subsequently heated to approximately 120 °C (oil bath temperature) for 0.5 h. Propargyl bromide (13 mL, 80% w/w solution in toluene, 14 g, 115 mmol) was added to the resulting cooled (oil bath temperature at approximately 100 °C) orange mixture at such a rate that steady reflux was allowed to occur with concommitant $NH_3$ evolution. Upon complete addition (0.5 h), the mixture was cooled slowly to room temperature and was then hydrolyzed cautiously by addition of water (100 mL). The toluene layer was separated and the aqueous layer was extracted with toluene (2 x 50 mL). The combined organics were dried ($MgSO_4$), filtered and reduced *in vacuo* to a brown oil that was taken up in $Et_2O$ (50 mL). 2 M HCl in $Et_2O$ was added to the ethereal solution of the oil. Trituration afforded a brown solid attempted recrystallization of which, from EtOH/$Et_2O$ gave an impure brown oil. The solvents were removed by rotary evaporation and the free base was prepared by addition of 2 M NaOH solution until pH 8-9. The organics were extracted into $Et_2O$ (3 x 100 mL) to give a light brown solution. Back-extraction into 1 M HCl (3 x 50 mL) gave a light yellow solution. The water was removed by rotary evaporation, then lyophilization to give 5.3 g of a light brown gum. Recrystallization from EtOH/$Et_2O$ afforded pure 2-pyrrolidin-l-yl-1 p-tolyl-pent-4-yn-l-one, as its hydrogen chloride salt (3.15 g, 11%): Mp 178 °C (dec.); $^1$H NMR δ 10.6 - 10.4 (br, 1H), 7.97 (d, 2H), 7.45 (d, 2H), 5.66 (m, 1H), 3.7 - 3.2 (m, 3H), 3.2 - 2.9 (m, 4H), 2.43 (s, 3H), 2.1-1.8 (m, 4H); $^{13}$C NMR δ 193.9, 146.0, 131.1, 129.7, 129.2, 76.8, 76.6, 65.2, 54.0, 52.0, 22,9, 22.9, 21.3,20.0; APCI MS *m/z* 242 (M + 1); Anal. ($C_{16}H_{20}ClNO$) C, H, N, Cl.

*Example 4*

**1-(4-Hydroxymethyl-phenyl)-2-pyrrolidin-l-yl-pentan-l-one, hydrogen chloride salt.**

This compound was prepared, in 79% yield, as described in General Procedure A, with slight modifications; Mp 186 - 187 °C (dec.); $^{1}H$ NMR δ 10.6 - 10.4 (br, 1H), 8.05 (d, 2H), 7.56 (d, 2H), 5.7 - 5.4 (br, m, 2H), 4.62 (s, 2H), 3.7 - 3.55 (m, 1 H), 3.55 - 3.3 (m, 1 H), 3.35 - 3.15 (m, 1 H), 3.1 - 3.0 (m, 1 H), 2.1 - 1.8 (m, 6H), 1.3 - 1.15 (m, 1H), 1.15 - 0.95 (m, 1H), 0.78 (t, $J$= 7 Hz, 3H); $^{13}C$ NMR δ 196.2, 150.4, 132.8, 128.8, 126.7, 67.4, 62.2, 53.8, 51.9, 31.8, 22.8, 17.3, 13.7; MS 262; Anal. ($C_{16}H_{24}ClNO_2.1/4H_20$) C, H, N, Cl.

*Example 5*

**1-Phenyl-3-pyrrolidin-1-yl-2 p-tolyl-hexan-2-ol, hydrogen chloride salt.** The pyrovalerone (2.0 g, 7.1 mmol) was freed from its HCI salt by treatment with 20% $Na_2CO_3$ and extraction of the organics into $Et_2O$. The $Et_2O$ extracts were dried ($MgS0_4$), filtered and reduced *in vacuo* to a pale yellow oil. This oil was taken up in toluene (20 mL) and cooled on an ice bath. Benzylmagnesium chloride (3.9 mL, 2.0 M solution in THF, 7.8 mmol, 1.1 mol eq.) was addedvia syringe over 5 min to the solution which was subsequently hydrolyzed by addition of 1 M HCI (20 mL). The resulting flocculent white precipitate was collected by filtration, washed with 1 M HCI (5 mL), then $Et_2O$ (50 mL), dried under suction, then in air. Recrystallization from EtOH/$Et_2O$ afforded pure 1-phenyl-3-pyrrolidin-l-yl-2-p-tolyl-hexan-2-ol, as its hydrogen chloride salt (2.0 g, 75%): Mp 211 °C (dec.); $^{1}H$ NMR δ 9.5 - 9.3 (br, 1H), 7.41 (d, 2H), 7.2 - 7.0 (m, 7H), 6.07 (s, 1H), 3.85 - 3.6 (br, m, 2H), 3.41 (m, 2H), 3.15 - 2.9 (m, 2H), 3.8 - 3.6 (m, 1H), 2.25 (s, 3H), 1.95 - 1.75 (br, m, 5H), 1.4 - 1.1 (m, 2H), 1.1 - 0.9 (m, 1H), 0.78 (t, 311); $^{13}C$ NMR δ 137.7, 136.4, 136.2, 130.8, 128.3, 127.3, 126.7, 125.8, 77.6, 72.0, 55.9, 44.0, 26.3, 24.4, 22.6, 22.2, 20.6, 14.0; APCI MS $m/z$ 338 (M + 1); Anal. ($C_{23}H_{32}C1NO$) C, H, N, Cl.

*Example 6*

**2-Pyrrolidin-1-yl-1 p-tolyl-pent-4-ene-l-one, hydrogen chloride salt.** This compound was prepared as described previously[x]; Mp 196 °C (dec.); $^{1}H$ NMR δ 10.8 - 10.6 (br, 1H), 7.96 (d, 2H), 7.43 (d, 2H), 5.8 - 5.6 (m, 2H), 5.03 (s, 1H), 5.00 (m, 1H), 3.75 - 3.6 (br, 1H), 3.6 - 3.4 (br, I H), 3.4 - 3.2 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 3.85 - 3.65 (br, m, 2H), 2.42 (s, 3H), 2.2 - 1.85 (br, m, 4H);$^{13}C$ NMR δ 195.2, 145.8, 131.8, 130.6, 129.7, 129.0, 120.1, 66.9, 53.8, 52.0, 34.2, 22.9, 21.3; APCI MS $m/z$ 244 (M + 1); Anal. ($C_{16}H_{22}C1NO$) C, H, N, Cl.

*Example 7*

**1-(3,4-Dichloro-phenyl)-2-pyrrolidin-1 -yl-pent-4-ene-l -one, hydrogen chloride salt.** This compound was prepared as described previously; Mp 176 °C (dec.); $^{1}H$ NMR δ 10.8 - 10.6

(br, 1H), 8.29 (d, 1 H), 8.00 (dd, 1 H), 7.94 (d, 1 H), 5.8 - 5.6 (m, 2H), 5.07 (s, 1 H), 5.02 (m, 1 H), 3.75 - 3.6 (br, m, 1 H), 3.6 - 3.3 (br, m, 1H), 3.3 - 3.1 (br, m, 2H), 2.77 (m, 2H), 2.2 - 1.8 (br, m, 4H), $^{13}$C NMR δ 194.2, 137.8, 134.4, 132.2, 131.6, 130.8, 130.3, 128.8, 120.6, 67.2, 53.9, 52.1, 33.8, 22.9; APCI MS *m/z* (relative intensity):302 ((M + 1), 100%), 300,298; Anal. ($C_{15}H_{18}C1_3NO$) C, H, N, Cl.

*Example 8*

**4-(2-Pyrrolidin-1-yl-pentanoyl)-benzoic acid methyl ester, hydrogen chlroride salt.** This compound was prepared, in 77% yield, as described in General Procedure A, with slight modifications; Mp 202 °C (dec.); $^1$H NMR δ 10.7 - 10.5 (br, 1H), 8.3 - 8.1 (m, 4H), 5.58 (m, 1H), 3.91 (s, 3H), 3.7 - 3.5 (br, m, 2H), 3.3 - 3.05 (br, m, 2H), 2.15 - 2.85 (br, m, 6H), 1.4 - 1.2 (m, 1H), 1.15 - 0.95 (m, 1H), 0.77 (t, *J*= 7 Hz, 3H); $^{13}$C NMR δ 196.5, 165.3, 137.6, 134.6, 129.8, 129.2, 67.9, 53.9, 52.7, 51.9, 31.4, 22.9, 17.2, 13.7; APCI MS *m/z* (relative intensity): 290 ((M + 1), 100%), 275; Anal. ($C_{17}H_{24}C1N0_3$) C, H, N, Cl.

*Example 9*

0-2536 **1-(2-Bromo-4,5-dimethoxy-phenyl)-2-pyrrolidin-1-yl-pentan- 1 -one, hydrogen chloride salt.** This compound was prepared, in 68% yield, as described in General Procedure A, however, the final compound, which contained residual $Et_2O$ that could not be romoved by further recrystallization, was dissolved in $H_2O$ lyophilized; Mp 100 - 120°C (dec.); $^1$H NMR δ 10.6 - 10.4 (br, 1H), 7.59 (s, 1H), 7.35 (s, 1H), 5.58 (br, 1 H), 3.89 (s, 6H), 3.7 - 3.55 (br, 2H), 3.3 - 3.15 (br, m, 2H), 2.15 - 1.7 (m, 6H), 1.4 - 1.2 (m, 1 H), 1.2 - 1.0 (m, 1H), 0.79 (t, *J*= 7 Hz, 3H); $^{13}$C NMR δ 196.2, 152.5, 147.9, 127.3, 117.7, 113.7, 112.2, 69.4, 56.6, 56.3, 51.7, 31.2, 22.9, 17.2, 13.7; APCI MS *m/z* 372, 370 (Br2) (M + 1); Anal. ($C_{17}H_{25}BrClN0_3.2/3H_20$) C, H, N, Cl.

*Example 10*

0-2529 and 0-2530 - **2-Pyrrolidin-1-yl p-tolyl-pentan-l-ol, hydrogen chloride salt and 2-Pyrrolidin-1-yl p-tolyl-pentan-l-ol, hydrogen chloride salt.** (DIASTEREOISOMER 2 - 0-2530). Pyrovalerone, hydrogen chloride salt (1.50 g, 5.32 mmol) was suspended in THF (20 mL). $LiAlH_4$ (0.20 g, 5.3 mmol) was added in several small portions at room temperature to the stirring mixture with slight heat evolution. The resulting clear solution was hydrolyzed cautiously with $H_2O$, then made acidic by addition of lM aqueous HCl. The aqueous extracts were collected and basified to pH 8-9 with 20% aqueous $Na_2CO_3$. The organics were extracted

into $Et_20$, dried ($MgSO_4$), filtered, and reduced to an oil *in vacuo*. Chromatography (5% $NEt_3$/15% EtOAc/80% hexanes) gave the two diastereoisomers. The hydrogen chloride salts were prepared from 2M ethereal HCl and recrystallized from EtOH/$Et_2O$ to afford 2-Pyrrolidin-l-yl p-tolyl-pentan-l-ol, hydrogen chloride salt (DIASTEREOISOMER 1, 0-2529), a colorless crystalline solid (0.57 g, 37%); Mp 140 - 142°C; $^1$H NMR δ 10.15 - 10.0 (br, 1 H), 7.32 (d, 2H), 7.19 (d, 2H), 6.20 (d, $J$ = 5 Hz, 1 H), 5.24 (s, 1 H), 3.75 - 3.65 (br, m, 1H), 3.65 - 3.5 (br, m, 111), 3.4 - 3.3 (br, 2H), 3.2 - 3.05 (br, m, 1H), 2.30 (s, 3H), 2.1 - 1.8 (br, m, 4H), 1.75 - 1.6 (m, 1H), 1.4 - 1.25 (br, m, 1H), 1.1 - 0.95 (m, 1H), 0.8 - 0.6 (m, 1H), 0.57 (t, $J$= 7 Hz, 3H); $^{13}$C NMR δ 136.2, 128.6, 125.5, 69.3, 68.1, 51.5, 26.5, 22.7, 22.5, 20.7, 20.3, 13.7; APCI MS *m/z* 248 (M + 1); Anal. ($C_{16}H_{26}C1NO$) C, H, N, Cl. and 2-Pyrrolidin-1-yl p-tolyl-pentan-l-ol, as its hydrogen chloride salt (x), a colorless microcrystalline solid (159 mg, 10%) (DIASTEREOISOMER 2 - 0-2530, this was the more polar material also); Mp 219°C (dec.); $^1$H NMR δ 9.8 - 9.65 (br, 1H), 7.33 (d, 2H), 7.20 (d, 2H), 6.53 (d, $J$ = 4 Hz, I H), 4.65 (dd $J$ = 4,9 Hz, 1H), 3.55 - 3.3 (m, 3H), 3.3 - 3.15 (br, m, 1H), 3.15 - 2.95 (br, m, I H), 2.31 (s, 3H), 2.0 - 1.85 (br, 4H), 1.55 - 1.35 (br, m, 2H), 1.05 - 0.85 (m, 1H), 1.75 - 1.6 (m, 4H);$^{13}$C NMR δ 138.4, 137.3, 128.9, 127.1, 72.1, 67.0, 40.3, 40.1, 27.6,23.3,23.0,20.8,20.0,13.6; APCI MS *m/z* 248 (M + 1); Anal. ($C_{16}H_{26}C1NO$) C, H, N, Cl.

*Example 11*

0-2537 **1-(4-Propynyl-phenyl)-2-pyrrolidin-1-yl-pentan-1-one, hydrogen chloride salt.** 1-(4-Iodo-phenyl)-2-pyrrolidin-l-yl-pentan-l-one, hydrogen chloride salt (500 mg, 1.27 mmol) was taken up in $Et_2NH$ (10 mL) and degassed by purging with $N_2$. [$PdCl_2(PPh_3)_2$] (18 mg, $2.5.10^{-5}$ mol) and Cul (2.4 mg, $1.3.10^{-5}$ mol) were added to the stirring solution at room temperature. Propyne was then bubbled through the resulting yellow mixture for 7 h. The mixture was filtered and reduced to an oil *in vacuo*. The oil was taken up in $Et_2O$ and extracted into 1M aqueous HCI, then back-extracted into $Et_2O$ by treatment with 20% aqueous $Na_2CO_3$ until pH 8-9. The organic extracts were dried ($MgSO_4$), filtered, and reduced to a pale yellow oil *in vacuo*. The hydrogen chloride salt was prepared from 2M ethereal HCI and recrystallized twice from EtOH/$Et_2O$ to give pure 1-(4-Propynyl-phenyl)-2-pyrrolidin-l-yl-pentan-l-one, as a colorless crystalline solid (260 mg, 67%). Mp 231 °C (dec.); $^1$H NMR δ 10.6 - 10.4 (br, IH), 8.04 (d, 2H), 7.62 (d, 2H), 5.55 - 5.4 (br, m, 1H), 3.7 - 3.55 (br, 1H), 3.55 - 3.4 (br, 111), 3.3 - 3.1 (br, m, 114), 3.1 - 2.95 (br, m, I H), 2.12 (s, 3H), 2.1 - 1.8 (br, m, 6H), 1.3 - 1.15 (m, 1H), 1.15 - 0.95

(m, 1H), 0.78 (t, $J$= 7 Hz, 3H); $^{13}$C NMR δ 195.9, 133.1, 131.9, 129.9, 129.1, 92.1, 79.0, 67.5, 53.8, 51.9, 31.7, 22.8, 17.2, 13.7, 4.1; APCI MS $m/z$ 270 (M + 1); Anal. ($C_{18}H_{24}C1NO$) C, H, N, Cl.

*Example 12*

0-2512 **1-(3,4-Dimethoxy-phenyl)-2-pyrrolidin-1-yl-pentan-1 -one, hydrogen chloride salt.** This compound was prepared, in 74% yield, as described in General Procedure A, with slight modifications; Mp 177°C (dec.); $^{1}$H NMR δ 10.5 - 10.3 (br, 1H), 7.78 (d, IH), 7.53 (d, 1H), 7.18 (d, 1H), 5.55 - 5.4 (br, m, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.7 - 3.55 (br, m, 1H), 3.5 - 3.3 (br, m, 1H), 3.3 - 3.15 (br, m, 1H), 3.05 - 2.9 (br, m, 1H), 2.1 - 1.8 (m, 6H), 1.3 - 1.0 (m, 2H), 0.80 (t, $J$= 7 Hz, 3H); $^{13}$C NMR δ 194.7, 154.7, 149.0, 127.2, 124.6, 111.2, 110.5, 66.7, 56.0, 55.7, 53.7, 51.8, 32.1, 22.8,17.4,13.7; APCI MS $m/z$ 292 (M + 1); Anal. ($C_{17}H_{26}C1N0_3$) C, H, N, Cl.

*Example 13*

0-2494 **4-Methyl-2-pyrrolidin-1-yl-1 p-tolyl-pentan-1-one, hydrogen chloride salt.** This compound was prepared, in 68% yield, as described in General Procedure A, with slight modifications; Mp 218°C (dec.); $^{1}$H NMR δ 10.9 - 10.75 (br, 1H), 8.06 (d, 2H), 7.45 (d, 2H), 5.46 (m, 1 H), 3.75 - 3.6 (br, 1 H), 3.6 - 3.4 (br, 1 H), 3.3 - 3.0 (br, m, 2H), 2.42 (s, 3H), 2.1 - 1.7 (m, 6H), 1.45 - 1.3 (m, 1 H), 0.82 (dd, $J$ = 2, 6 Hz, 6H); $^{13}$C NMR δ 197.2, 164.0, 132.9, 129.9, 129.0, 64.4, *52.7, 51.2,* 24.2, 23.3, 22.8, 21.5, 21.3; APCI MS $m/z$ 260 (M + 1); Anal. ($C_{17}H_{26}ClNO$) C, H, N, Cl.

*Example 14*

0-2493 **1-(4-Iodo-phenyl)-2-pyrrolidin-1-yl-pentan-1-one, hydrogen chloride salt.** This compound was prepared, in 37% yield, as described in General Procedure A, with slight modifications; Mp 218°C (dec.);$^{1}$H NMR δ 10.75 - 10.65 (br, 111), 8.05 (d, 2H), 7.84 (d, 2H), 5.53 (m, 1H), 3.7 - 3.65 (br, 1H), 3.65 - 3.5 (br, m, 1H), 3.3 - 3.15 (br, m, I H), 3.15 - 3.0 (br, m, 1H), 2.1 - 1.8 (br, m, 6H), 1.35 - 1.15 (m, I H), 1.15 - 0.95 (m, 1H), 0.78 (t, $J$ = 7 Hz, 3H); $^{13}$C NMR δ 196.3, 138.2, 133.6, 130.3, 104.6, 67.3, 53.7, 51.9, 31.6, 22.9, 17.3, 13.7; APCI MS $m/z$ 358 (M + 1); Anal. ($C_{15}H_{21}C1INO$) C, H, N, Cl.

*Example 15*

0-2482 **1 -Naphthalen-2-yl-2-pyrrolidin-1 -yl-pentan- 1 -one, hydrogen chloride salt.** This compound was prepared, in 51 % yield, as described in General Procedure A, with slight

modifications; Mp 221 - 223°C (dec.); $^1$H NMR δ 10.8 - 10.6 (br, 1H), 8.92 (s, 1H), 8.2 - 8.0 (m, 4H), 7.75 (dt, 2H), 5.73 (m, 1H), 3.75 - 3.6 (br, 1H), 3.6 - 3.4 (br, m, 1H), 3.35 - 3.1 (br, m, 2H), 2.2 - 1.8 (m, 6H), 1.4 - 1.2 (m, 1H), 1.2 - 1.0 (m, 1 H), 0.78 (t, $J$ = 7 Hz, 3H); $^{13}$C NMR δ 196.6, 135.7, 132.0, 131.8, 131.7, 129.9, 129.7, 129.0, 127.8, 127.5, 123.4, 67.3, 53.6, 52.0. 31.9, 22.9, 17.4, 13.7; APCI MS *m/z* 282 (M + 1); Anal. ($C_{19}H_{24}ClNO$) C, H, N, Cl.

*Example 16*

0-2481 **2-Pyrrolidin-1-yl-1-(4-trifluoromethyl-phenyl)-pentan-l-one, hydrogen chloride salt.** This compound was prepared, in 44% yield, as described in General Procedure A, with slight modifications; Mp 228°C (dec.); $^1$H NMR δ 10.8 - 10.6 (br, 1H), 8.28 (d, 2H), 8.03 (d, 2H), 5.62 (m, 1H), 3.7 - 3.4 (br, m, 2H), 3.3 - 3.05 (br, m, 2H), 2.1 - 1.8 (br, m, 6H), 1.4 - 1.2 (m, 1H), 1.1 - 0.9 (m, 1H), 0.78 (t, $J$= 7 Hz, 3H); $^{13}$C NMR δ 196.2, 137.4, 129.7, 126.3, 67.8, 51.9, 31.3, 22.9, 17.2, 13.7; APCI MS *m/z* 300 (M + 1); Anal. ($C_{16}H_{21}C1F_3NO$) C, H, N, Cl.

*Example 17*

0-2480 **2-Pyrrolidin-1-yl-l-m-tolyl-pentan-1-one, hydrogen chloride salt.** This compound was prepared, in 53% yield, as described in General Procedure A, with slight modifications; Mp 166°C (dec.); $^1$H NMR δ 10.8 - 10.6 (br, 1H), 7.90 (d, 2H), 7.65 - 7.5 (m, 2H), 5.57 (m, 1H), 3.7 - 3.55 (br, 1H), 3.55 - 3.4 (br, 1H), 3.3 - 3.15 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 2.42 (s, 3H), 2.1 - 1.8 (br, m, 6H), 1.35 - 1.15 (m, 1H), 1.15 - 0.95 (m, 1H), 0.78 (t, $J$ = 7 Hz, 3H); $^{13}$C NMR δ 196.7, 138.8, 135.6, 134.5, 129.1, 126.1, 67.4, 53.6, 51.9, 31.7, 22.9, 20.8, 17.3, 13.7; APCI MS *m/z* 246 (M + 1); Anal. ($C_{16}H_{24}C1NO$) C, H, N, Cl.

*Example 18*

0-2479 **2-Pyrrolidin-1-yl-1-o-tolyl-pentan-1-one, hydrogen chloride salt.** This compound was prepared, in 39% yield, as described in General Procedure A, however, we were unable to obtain a crystalline sample of the compound. The hydrogen chloride salt was taken up in $H_2O$ and lyophilized; $^1$H NMR δ 10.9 - 10.7 (br, 1H), 8.12 (d, 1H), 7.58 (t, 1H), 7.44 (t, 2H), 5.56 (m, 1H), 3.7 - 3.5 (br, 2H), 3.35 - 3.1 (br, m, 2H), 2.46 (s, 3H), 2.1 - 1.7 (br, m, 6H), 1.4 - 1.2 (m, 1H), 1.1 - 0.9 (m, 1H), 0.76 (t, $J$ = 7 Hz, 3H); $^{13}$C NMR δ 199.1, 138.8, 134.4, 133.2, 132.3, 130.0, 126.2, 68.9, 53.5, 51.8, 31.4, 23.0, 20.7, 17.5, 13.7; APCI MS *m/z* 246 (M + 1); Anal. ($C_{16}H_{24}C1NO.92/100H_20$) C, H, N, Cl.

*Example 19*

0-2477 **2-Pyrrolidin-l-yl-methyl-1 p-tolyl-pentan-l-one, hydrogen chloride salt.** This

compound was prepared from 1-*o*-Tolyl-pentan-l-one (3.5 g, 20 mmol) using the same method as described for (x) with the following modifications. No chromatography was performed. The hydrogen chloride salt of the crude free base isolated after extraction of the crude reaction mixture into 1 M aqueous HCl and back-extraction (with 20% aqueous $Na_2CO_3$) into $Et_2O$ in the usual way, was recrystallized from EtOH/$Et_2O$ to give pure crystalline 2-pyrrolidin-l-yl-methyl-1 *p*-tolyl-pentan-l-one, as its hydrogen chloride salt (x) (2.6 g, 44%).Mp 176°C (dec.); $^1$H NMR δ 10.8 - 10.6 (br, 1H), 7.98 (d, 2H), 7.39 (d, 2H), 4.25 - 4.15 (br, m, 1H), 3.65 - 3.5 (m, 2H), 3.5 - 3.25 (m, 2H), 3.1 - 2.95 (br, m, 1H), 2.95 - 2.8 (br, m, 1H), 2.40 (s, 3H), 2.0 - 1.75 (m, 4H), 1.7 - 1.4 (m, 2H), 1.3 - 1.1 (m, 2H), 0.81 (t, $J$ = 7 Hz, 3H); $^{13}$C NMR δ 200.4, 144.4, 135.2, 129.7, 129.5, 128.7, 128.5, 54.0, 53.7, 53.3, 41.9, 33.5, 22.8, 22.3, 21.1, 19.0, 13.8; APCI MS *m/z* 260 (M + 1); Anal. ($C_{17}H_{26}ClNO$) C, H, N, Cl.

*Example 20*

0-2478 **1-(3,4-Dichloro-phenyl)-2-pyrrolidin-1-yl-methyl-pentan-1-one, hydrogen chloride salt.** 2-Bromo-l-(3,4-dichloro-phenyl)-pentan-l-one (3.5 g, 15 mmol), pyrrolidine.HC1(2.4 g, 23 mmol) and paraformaldehyde (1.35 g, 45 mmol) were taken up in $^i$PrOH (25 mL) containing concentrated HCI (0.2 mL). The mixture was refluxed for 16 h. The solvent was removed by rotary evaporation and the residue was separated between 1 M aqueous HCI and $Et_2O$. The aqueous extracts were basified with 20% aqueous $Na_2CO_3$ to pH 8-9 and the organics were extracted into $Et_2O$. The organics were dried ($MgSO_4$), filtered, and reduced to an oil *in vacuo*. Column chromatography (10% McOH/$CH_2Cl_2$) gave the pure free base. The hydrogen chloride salt was prepared by reaction with 2 M ethereal HCI and filtration of the resulting white precipitate. Thus, 1-(3,4-Dichloro-phenyl)-2-pyrrolidin-1-yl-methyl-pentan-l-one, hydrogen chloride salt (0.61 g, 12%). Mp 168°C (dec.); $^1$H NMR δ 10.7 - 10.5 (br, 1H), 8.29 (d, 1H), 8.05 (dd, 1H), 7.88 (d, 1H), 4.3 - 4.1 (br, 1H), 3.7 - 3.5 (br, m, 2H), 3.5 - 3.25 (br, m, 2H), 3.15 - 2.85 (br, m, 2H), 2.1 - 1.75 (br, m, 4H), 1.75 - 1.4 (m, 2H), 1.35 - 1.05 (m, 2H), 0.81 (t, $J$ = 7 Hz, 3H);$^{13}$C NMR δ 198.9, 136.6, 135.9, 132.1, 131.4, 131.2, 130.5, 130.3, 128.7, 128.5, 54.1, 53.4, 42.3, 42.2, 33.1, 22.7, 22.4, 18.8, 13.8; APCI MS *m/z* 314, 312, 310 (M + 1); Anal. ($C_{16}H_{22}Cl_3NO$) C, H, N, Cl.

*Example 21*

0-2446 2-**Pyrrolidin-1-yl-1-(4-N-methylpyrrole-phenyl)-pentan-1-one, hydrogen chloride salt.** A cooled (-78°C) solution of *N*-Methylpyrrole (1.14 g, 14 mmol) in THF (10 mL)

was treated with $^tBuLi$ (9.1 mL of a 1.7M solution in pentane, 15 mmol) in a drop-wise fashion. The mixture was then warmed to room temperature for 2 h, then cooled to -78°C. Chlorotributylstannane (5.0 g, 15 mmol) was added to the mixture in a drop-wise fashion. On completion of addition, the mixture was warmed to room temperature and stirred for I h. The mixture was filtered and reduced to an oil *in vacuo.* This oil (crude 2-tributylstannyl-(N-methylpyrrole)) was added to a solution of 2-Pyrrolidin-l-yl-1-(4'-bromo-phenyl)-pentan-l-one (which had been freed from its hydrogen chloride salt by treatment with 20% aqueous .$Na_2CO_3$ and extraction into $Et_2O$) in dioxane (30 mL). The resulting solution was degassed by purging with $N_2$. $[Pd(PPh_3)_4]$ (264 mg, 0.22 mmol) was added and the mixture was heated to 95 - 100°C (oil bath temperature) for a period of 10 h. The solvent was removed *in vacuo.* The pure free base was obtained by column chromatography (5% $McOH/CH_2C1_2$) as a yellow oil. The hydrogen chloride salt was prepared by treatment with 2M ethereal HCI. Lyophilization of an aqueous solution of the salt afforded a pale green solid characterized as 2-Pyrrolidin-l-yl-1-(4-*N*-methylpyrrole-phenyl)-pentan-1-one, as its hydrogen chloride salt (1.4 g, 36%). $^1H$ NMR δ 10.6 - 10.45 (br, IH), 8.11 (d, 2H), 7.72 (d, 2H), 7.00 (dd, 1H), 6.45 (dd, 1H), 6.15 (dd, 1H), 5.54 (m, 1H), 3.77 (s, 3H), 3.7 - 3.55 (br, 1H), 3.55 - 3.4 (br, 1H), 3.35 - 3.15 (br, m, IH), 3.15 - 3.0 (br, m, IH), 2.1 - 1.85 (br, m, 6H), 1.35 - 1.2 (m, 1H), 1.2 - 1.0 (m, 1H), 0.82 (t, $J$= 7 Hz, 3H); $^{13}C$ NMR δ 195.6, 139.1, 131.9, 131.5, 129.4, 127.4, 127.1, 111.1, 108.2, 67.2, 53.7, 51.9, 35.6, 31.9, 22.9, 17.4, 13.7; APCI MS *m/z* 311 (M + 1); Anal. ($C_{20}H_{27}C1N_20.2/3H_20$) C, H, N, Cl.

*Example 22*

0-2438 **2-Pyrrolidin-1-yl-1-(4-thiophen-2-yl-phenyl)-pentan-1-one, hydrogen chloride salt.** This compound was prepared using a procedure analogous to that described for the preparation of (x), except that commercially available 2-tributylstannyl thiophene was employed as a starting material, and chromatography was not performed on the crude free base. The crude hydrogen chloride salt was readily obtained by treatment of the crude free base with 2M ethereal HCI. Recrystallization from hot EtOH gave pure (x) as a colorless crystalline solid (1.23 g, 61%). Mp 220°C (dec.); $^1H$ NMR (DMSO-d6 + 12 drops $CD_3OH$) δ 8.12 (d, 2H), 7.93 (d, 2H), 7.77 (dd, 1 H), 7.72 (dd, 1 H), 7.23 (dd, 1 H), 5.5 - 5.4 (br, I H), 3.7 - 3.45 (br, m, 2H), 3.3 - 3.2 (br, m, 1H), 3.1 - 3.0 (br, m, 1H), 2.2 - 1.9 (br, m, 6H), 1.35 - 1.2 (m, 1H), 1.2 - 1.0 (m, IH), 0.83 (t, $J$ = 7 Hz, 3H); $^{13}C$ NMR δ 195.9, 141.8, 140.3, 132.9, 130.3, 129.3, 128.6, 126.6, 126.0, 68.1, 54.5, 52.1, 32.2, 23.1, 17.4, 13.8; APCI MS *m/z* 314 (M + 1); Anal. ($C_{19}H_{24}C1NOS$) C, H, N, Cl.

*Example 23*

0-2441 **2-Pyrrolidin-1-yl-1-(4-furan-2-yl-phenyl)-pentan-l-one, hydrogen chloride salt.** This compound was prepared using a procedure analogous to that previously described except that commercially available 2-tributylstannyl furan was employed as a starting material, and chromatography was not performed on the crude free base. The crude hydrogen chloride salt was recrystallized from hot EtOH to give pure (1.13 g, 59%) as a colorless crystalline solid Mp 236°C (dec.); $^1$H NMR (DMSO-d6 + 6 drops $CD_3OH$) δ 8.14 (d, 2H), 7.95 (d, 2H), 7.90 (d, 1 H), 7.29 (d, 1 H), 6.71 (dd, 1 H), 5.51 (m, 1 H), 3.7 - 3.6 (br, m, 1 H), 3.6 - 3.45 (br, m, 1 H), 3.35 - 3.2 (br, m, 1 H), 3.15 - 3.0 (br, m, 1 H), 2.15 - 1.85 (br, m, 6H), 1.35 - 1.15 (m, 1 H), 1.15 - 1.0 (m, 1H), 0.81 (t, $J$ = 7 Hz, 3H); $^{13}$C NMR δ 195.7, 151.8, 145.1, 136.0, 132.6, 130.0, 123.8, 112.9, 109.9, 67.8, 54.2, 52.0, 32.0, 22.9, 17.3, 13.7; APCI MS *m/z* 298 (M + 1); Anal. ($C_{19}H_{24}ClNO_2$) C, H, N, Cl.

*Example 24*

0-2443 **2-Pyrrolidin-1-yl-1-(4-nitro-phenyl)-pentan-1-one, hydrogen chloride salt.** A 50% w/w aqueous solution of $H_2O_2$(7 mL, 0.12 mol) was added to $CH_2Cl_2$, (50 mL which had been cooled on an ice bath. Trifluoroacetic anhydride (23 mL, 0.14 mol) was added slowly *via* syringe, then the solution was warmed to room temperature. *N*-[4-(2-Pyrrolidin-1-yl-pentanoyl)-phenyl]-acetamide, hydrogen chloride salt (4.5 g, 18 mmol) was added over 20 min, then the mixture was heated to reflux for 1 h. The solution was cooled, then quenched cautiously with aqueous $Na_2SO_3$ (100 mL of a 1.6 M solution, 0.16 mol). The organics were separated and extracted into $Et_2O$, then back-extracted into 1 M aqueous HCl. The acidic extracts were basified with 20% aqueous $Na_2CO_3$ to pH 8-9 and extracted into $Et_2O$. The organic extracts were dried ($MgSO_4$), filtered, then treated with 2 M ethereal HCl. The resulting white precipitate was collected on a frit, dissolved in water, then lyophilized to give pure 2-Pyrrolidin-l-yl-1-(4-nitro-phenyl)-pentan-l-one, as its hydrogen chloride salt (x) (290 mg, 5%). Mp 189°C (dec.);$^1$H NMR δ 10.8 - 10.6 (br, 1H), 8.45 (d, 2H), 8.32 (d, 2H), 5.65 (m, 1H), 3.7 - 3.3 (br, m, 2H), 3.3 - 3.1 (br, m, 2H), 2.1 - 1.8 (br, m, 6H), 1.4 - 1.2 (m, 1H), 1.1 - 0.9 (m, 1H), 0.78 (t, $J$ = 7 Hz, 3H); $^{13}$C NMR δ 196.0, 150.8, 138.7, 130.4, 124.3, 68.1, 53.9, 52.0, 31.2, 22.9, 17.2, 13.7; APCI MS *m/z* 277 (M + 1); Anal. ($C_{15}H_{21}ClN_2O_3$.42/100$H_2O$.8/100HCl) C, H, N, Cl.

*Example 25*

0-2439 ***N*-[4-(2-Pyrrolidin-1-yl-pentanoyl)-phenyl]-acetamide, hydrogen chloride**

salt. This compound was prepared, in 56% yield, as described in General Procedure A, with slight modifications; Mp 195°C (dec.); $^{1}$H NMR δ 10.76 (s, 1H), 10.55 - 10.35 (br, 1H), 8.05 (d, 2H), 7.85 (d, 2H), 5.5 - 5.4 (br, m, 1H), 3.7 - 3.55 (br, 1H), 3.5 - 3.3 (br, 1H), 3.3 - 3.15 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 2.13 (s, 3H), 2.1 - 1.8 (br m, 6H), 1.3 - 1.15 (m, 1H), 1.15 - 1.0 (m, 1H), 0.79 (t, $J$= 7 Hz, 3H); $^{13}$C NMR δ 194.8, 169.4, 145.4, 130.4, 128.8, 118.4, 67.0, 53.6, 51.9, 32.0, 24.2, 22.8, 17.4, 13.7; APCI MS *m/z* 289 (M + 1); Anal. ($C_{17}H_{25}ClN_2O_2.1/2H_2O$) C, H, N, Cl.

*Example 26*

0-2419 **2-Pyrrolidin-1-yl-1-(4'-bromo-phenyl)-pentan-l-one, hydrogen chloride salt.** This compound was prepared, in 62% yield, as described in General Procedure A, with slight modifications; Mp 200°C (dec.); $^{1}$H NMR δ 10.7 - 10.5 (br, 1 H), 8.03 (d, 2H), 7.87 (d, 2H), 5.56 (m, 1 H), 3.7 - 3.55 (br, m, 1 H), 3.55 - 3.4 (br, m, 1 H), 3.35 - 3.1 (br, m, 1 H), 3.1 - 3.0 (br, m, 1 H), 2.1 - 1.8 (br, m, 6H), 1.4 - 1.2 (m, 1 H), 1.15 - 0.95 (m, 1H), 0.78 (t, $J$= 7 Hz, 3H); $^{13}$C NMR δ 196.0, 133.4, 132.4, 130.8, 129.4, 67.4, 53.7, 51.9, 31.6, 22.9, 17.3, 13.7; APCI MS *m/z* 312, 310 (M + 1); Anal. ($C_{15}H_{21}BrClNO$) C, H, N, Cl.

*Example 27*

O-2418 **2-Pyrrolidin-1-yl-1-(4'-hydroxy-phenyl)-pentan-1-one, hydrogen chloride salt.** 2-Pyrrolidin-1-yl-1-(4'methoxy-phenyl)-pentan-1-one (9.00 g, 30,3 mmol) was freed from its hydrogen chloride salt by basification to pH 8-9 with 20% aqueous $Na_2CO_3$ and extraction into $CH_2Cl_2$. The free base was dissolved in $CH_2Cl_2$ (50 mL) and cooled to -78°C, whereon $BBr_3$ (90 mL, 1.0 M solution in $CH_2Cl_2$, 90 mmol) was added to the solution over 0.5 h. The mixture was stirred for a further 1 h before warming gradually to room temperature. The gummy mixture, which became difficult to stir was quenched after 2 h with saturated aqueous $NaHCO_3$ and the neutral organics were extracted into $CH_2Cl_2$. A white solid precipitated from the aqueous layer which was collected on a frit (1.8 g). Work-up of the organic layer in the usual way afforded a further 1 g of crude free base which was converted to its hydrogen chloride salt by reaction with 2 M ethereal HCl. The two solids were combined and recrystallized from hot ethanol to give pure 2-Pyrrolidin-1-yl-1-(4'-hydroxy-phenyl)-pentan-1-one, as its hydrogen chloride salt (2.9 g, 34%). Mp 235°C (dec.); $^{1}$H NMR ($CD_3OD$) $\delta$ 7.99 (d, 2H), 6.93 (d, 2H), 5.26 (t, $J$ = 5.5 Hz, 1H), 5.0 - 1.8 (s, br, 2H), 3.7 - 3.0 (br, 4H), 2.2 - 1.9 (br, m, 6H), 1.4 - 1.1 (m,

2H), 0.89 (t, $J$ = 7 Hz, 3H); $^{13}$C NMR $\delta$ 195.0, 156.8, 132.9, 127.3, 117.0, 69.8, 33.9, 24.1, 18.6, 14.2; APCI MS *m/z* 248 (M + 1); Anal. ($C_{15}H_{22}ClNO_2$) C, H, N, Cl.

*Example 28*

O-2417 **2-Pyrrolidin-1-yl-1-(4'methoxy-phenyl)-pentan-1-one, hydrogen chloride salt.** This compound was prepared 68% yield, as described in General Procedure A, with slight modifications; $^1$H NMR $\delta$ 10.8 - 10.6 (br, 1H), 8.10 (d, 2H), 7.15 (d, 2H), 5.55 (m, 1H), 3.89 (s, 3H), 3.7 - 3.55 (br, m, 1H), 3.55 - 3.4 (br, m, 1H), 3.3 - 3.15 (br, m, 1H), 3.1 - 2.95 (br, m, 1H), 2.15 - 1.85 (br, m, 6H), 1.34 - 1.15 (m, 1H), 1.15 - 1.0 (m, 1H), 0.79 (t, $J$ = 7 Hz, 3H); $^{13}$C NMR $\delta$ 194.7, 164.5, 131.4, 127.4, 114.5, 66.7, 55.8, 53.4, 51.8, 32.0, 22.9, 17.5,13.7; APCI MS *m/z* 262 (M + 1); Anal. ($C_{16}H_{24}ClNO_2$.1/2$H_2O$.1/2HCl) C, H, N, Cl.

*Example 29*

O-2525 **3-Pyrrolidin-1-yl-1-*p*-tolyl-pentan-1-one, hydrogen chloride salt.** This compound was prepared from 1-*p*-Tolyl-pent-2-en-1-one using exactly the same procedure as that described for (x). Mp 97°C (dec.); $^1$H NMR $\delta$ 11.1 - 10.9 (br, 1H), 7.94 (d, 2H), 7.38 (d, 2H), 3.9 - 3.75 (br, 1H), 3.7 - 3.6 (m, 1H), 3.6 - 3.3 (m, 3H), 3.15 - 2.95 (br, m, 2H), 1.96 (s, 3H), 2.0 - 1.8 (br, m, 5H), 1.8 - 1.6 (m, 1H), 0.88 (t, $J$ = 7 Hz, 3H); $^{13}$C NMR $\delta$ 196.2, 144.3, 133.5, 129.3, 128.3, 59.7, 50.7, 50.4, 37.9, 23.8, 22.9, 22.8, 21.2, 9.9; APCI MS *m/z* 246 (M + 1); Anal. ($C_{16}H_{24}ClNO$) C, H, N, Cl.

*Example 30*

O-2524 **1-(3,4-Dichloro-phenyl)-3-pyrrolidin-1-yl-pentan-1-one, hydrogen chloride salt.** 1-(3,4-Dichloro-phenyl)-pen-2-en-1-one (1.29 g, 5.63 mmol) was taken up in EtOH (10 mL), cooled on an ice bath, and degassed by purging with $N_2$. Pyrrolidine (0.80 g, 11 mmol) was added dropwise over 2 min. After 0.5 h, the ethanolic solution was separated between 1M aqueous HCl and $Et_2O$. The HCl extracts were collected and back-extracted into $Et_20$ by treatment with 20% aqueous $Na_2CO_3$. The ethereal extracts were dried ($MgSO_4$), filtered, and treated with 2M ethereal HCl. Laborious trituration afforded a white powder which was collected on a frit and washed copiously with $Et_2O$. This white powder was identified as 1-(3,4-Dichloro-phenyl)-2-pyrrolidin-1-yl-methyl-pentan-1-one, hydrogen chloride salt (0.99 g, 50%). Mp 104 - 107°C (dec.); $^1$H NMR $\delta$ 11.1 - 10.9 (br, 1H), 8.27 (d, 1H), 7.98 (dd, 1H), 7.87 (d, 1H), 3.9 - 3.35 (br, m, 5H), 3.15 - 2.95 (br, 2H), 2.05 - 1.8 (br, m, 5H), 1.8 - 1.6 (m, 1H), 0.90 (t, $J$ = 7

Hz, 3H); $^{13}$C NMR $\delta$ 195.0, 136.4, 136.1, 131.8, 131.1, 130.3, 128.1, 59.2, 50.7, 50.1, 38.2, 23.8, 22.9, 10.0; APCI MS *m/z* 300, 302, 304 (M + 1); Anal. ($C_{15}H_{20}Cl_3NO.1/3H_2O$) C, H, N, Cl.

*Example 31*

O-2495 **1-(3-Iodo-phenyl)-2-pyrrolidin-1-yl-pentan-1-one, hydrogen chloride salt.** This compound was prepared, in 20% yield, as described in General Procedure A, with slight modifications; Mp 203°C (dec.); $^{1}$H NMR $\delta$ 10.6 - 10.4 (br, 1H), 8.39 (s, 1H), 8.14 (d, 1H), 8.07 (d, 1H), 7.44 (t, 1H), 5.51 (m, 1H), 3.7 - 3.55 (br, m, 1H), 3.55 - 3.4 (br, m, 1H), 3.3 - 3.15 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 2.1 - 1.8 (br, m, 6H), 1.35 - 1.15 (m, 1H), 1.1 - 0.9 (m, 1H), 0.79 (t, $J$ = 7 Hz, 3H); $^{13}$C NMR $\delta$ 195.7, 143.3, 136.9, 136.1, 131.8, 131.3, 128.0, 95.7, 67.5, 53.8, 51.9, 31.5, 22.8, 17.2, 13.6; APCI MS *m/z* 358 (M + 1); Anal. ($C_{15}H_{21}ClINO$) C, H, N, Cl.

*Example 32*

O-2390 **2-Pyrrolidin-1-yl-1-(3,4-Dichloro-phenyl)-pentan-1-one, hydrogen chloride salt.** This compound was prepared, in 32% yield, as described in General Procedure A, with slight modifications; Mp 195°C (dec.);$^{1}$H NMR $\delta$ 10.8 - 10.6 (br, 1H), 8.35 (d, 1H), 8.04 (dd, 1H), 7.94 (d, 1H), 5.58 (m, 1H), 3.7 - 3.6 (br, 1H), 3.6 - 3.45 (br, m, 1H), 3.3 - 3.05 (br,m, 2H), 2.15 - 2.85 (br, m, 6H), 1.35 - 1.15 (m, 1H), 1.15 - 0.95 (m, 1H), 0.79 (t, $J$ = 7 Hz, 3H); $^{13}$C NMR $\delta$ 195.0,137.8, 134.5, 132.3, 131.6, 130.8, 128.8, 67.5, 53.7, 51.9, 31.4, 22.9, 17.2, 13.6; APCI MS *m/z* 300, 302, 304 (M + 1); Anal. ($C_{15}H_{20}Cl_3NO$) C, H, N, Cl.

*Example 33*

O-2389 **2-Butylamin-1-yl-1-(3,4-dichloro-phenyl)-pentan-1-one, hydrogen chloride salt.** This compound was prepared, in 69% yield, as described in General Procedure A, with slight modifications; Mp 185°C (dec.); $^{1}$H NMR $\delta$ 9.8 - 9.6 (br, 1H), 9.3 - 9.1 (br, 1H), 8.35 (d, 1H), 8.04 (dd, 1H), 7.91 (d, 1H), 5.4 - 5.25 (br, 1H), 3.05 - 2.75 (br, m, 2H), 2.05 - 1.8 (br, m, 2H), 1.8 - 1.6 (br, m, 2H), 1.4 - 1.2 (m, 3H), 1.2 - 1.0 (m, 1H), 0.88 (t, $J$ = 7 Hz, 3H), 0.78 (t, $J$ = 7 Hz, 3H); $^{13}$C NMR $\delta$ 194.8, 137.6, 134.3, 132.3, 131.5, 130.6, 128.7, 60.8, 45.7, 31.5, 27.4, 19.3, 17.2, 13.6, 13.5; APCI MS *m/z* 302, 304, 306 (M + 1); Anal. ($C_{15}H_{22}Cl_3NO$) C, H, N, Cl.

*Example 34*

O-2388 **2-Piperidin-1-yl-1-(3,4-dichloro-phenyl)-pentan-1-one, hydrogen chloride salt.** This compound was prepared, in 35% yield, as described in General Procedure A, with slight modifications; Mp 202°C (dec.); $^{1}$H NMR $\delta$ 10.5 - 10.3 (br, 1H), 8.40 (d, 1H), 8.10 (dd, 1H), 7.94 (d, 1H), 5.45 - 5.35 (br, m, 1H), 3.7 - 3.55 (br, m, 1H), 3.45 - 3.3 (br, m, 1H), 3.2 -

1.95 (br, m, 2H), 2.1 - 1.65 (br, m, 7H), 1.5 - 1.3 (br, 1H), 1.2 - 1.0 (br, m, 2H), 0.81 (t, $J = 7$ Hz, 3H); $^{13}$C NMR $\delta$ 195.3, 138.0, 135.3, 132.4, 131.6, 130.7, 128.8, 65.8, 52.0, 50.2, 29.3, 22.3, 22.0, 21.5, 17.8, 13.7; APCI MS *m/z* 314, 316, 318 (M + 1); Anal. ($C_{16}H_{22}Cl_3NO$) C, H, N, Cl.

*Example 35*

O-2387 **2-Pyrrolidin-1-yl-phenyl-pentan-1-one, hydrogen chloride salt.** This compound was prepared, in 50% yield, as described in General Procedure A, with slight modifications; Mp 173°C (dec.); $^1$H NMR $\delta$ 10.85 - 10.65 (br, 1H), 8.11 (d, 2H), 7.78 (t, 1H), 7.64 (t, 2H), 5.62 (m, 1H), 3.7 - 3.55 (br, 1H), 3.55 - 3.4 (br, m, 1H), 3.35 - 3.2 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 2.15 - 1.85 (br, m, 6H), 1.4 - 1.2 (m, 1H), 1.15 - 0.95 (m, 1H), 0.78 (t, $J = 7$ Hz, 3H); $^{13}$C NMR $\delta$ 196.7, 134.9, 134.5, 129.2, 128.8, 67.3, 53.6, 51.9, 31.7, 22.9, 17.4,13.7; APCI MS *m/z* 232 (M + 1); Anal. ($C_{15}H_{22}ClNO$) C, H, N, Cl.

*Example 36*

O-2384 **2-Pyrrolidin-1-yl-1-(3,4-dichloro-phenyl)-butan-1-one, hydrogen chloride salt.** This compound was prepared, in 71 % yield, as described in General Procedure A, with slight modifications; Mp 211 °C (dec.); $^1$H NMR $\delta$ 10.95 - 10.75 (br, 1H), 8.35 (d, 1H), 8.06 (dd, 1H), 7.92 (d, 1H), 5.75 - 5.65 (br, m, 1H), 3.65 - 3.35 (br, m, 2H), 3.3 - 3.1 (br, m, 1H), 2.15 - 1.9 (br, m, 6H),), 0.78 (t, $J = 7$ Hz, 3H); $^{13}$C NMR $\delta$ 194.7, 137.7, 134.5, 132.3, 131.6, 130.7, 128.8, 68.5, 53.7, 51.8, 23.0, 22.6, 8.4; APCI MS *m/z* 286, 288, 290 (M + 1); Anal. ($C_{14}H_{18}Cl_3NO$) C, H, N.

*Example 37*

O-2370 **2-Pyrrolidin-1-yl-1-(4'-fluoro-phenyl)-pentan-1-one, hydrogen chloride salt.** This compound was prepared, in 78% yield, as described in General Procedure A, with slight modifications; Mp 218°C (dec.);$^1$H NMR $\delta$ 10.7 - 10.5 (br, 1H), 8.19 (m, 2H), 7.49 (t, 2H), 5.6 - 5.5 (br, m, 111), 3.7 - 3.55 (br, 1H), 3.55 - 3.4 (br, 1H), 3.3 - 3.15 (br, m, 1H), 3.15 - 3.0 (br, 1H), 2.15 - 1.8 (br, m, 6H), 1.35 - 1.15 (m, 1H), 1.15 -0.95 (m, 1H), 0.79 (t, $J = 7$ Hz, 3H);$^{13}$C NMR $\delta$ 195.2, 132.2, 132.0, 131.3, 116.6, 116.3, 67.2, 53.5, 51.9, 31.7, 22.9, 17.4, 13.7; APCI MS *m/z* 250 (M + 1); Anal. ($C_{15}H_{21}ClFNO$) C, H, N, Cl.

*Example 38*

O-2371 **2-Pyrrolidin-1-yl-1-*p*-tolyl-pentan-1-one, hydrogen chloride salt.** This compound was prepared, in 68% yield, as described in General Procedure A, with slight modifications; Mp 180°C (dec.); $^1$H NMR $\delta$ 10.8 - 10.65 (br, 1H), 8.01 (d, 2H), 7.44 (d, 2H),

5.56 (m, 1H), 3.7 - 3.55 (br, 1H), 3.55 - 3.4 (br, m, 1H), 3.35 - 3.2 (br, m, 1H), 3.15 - 3.0 (br, m, 1H), 2.42 (s, 3H), 2.15 - 1.85 (br, m, 6H), 1.4 - 1.2 (m, 1H), 1.15 - 0.95 (m, 1H), 0.78 (t, $J = 7$ Hz, 3H); $^{13}C$ NMR $\delta$ 196.1, 145.8, 132.1, 129.8, 129.0, 67.1, 53.5, 51.9, 31.8, 22.9, 21.3, 17.4, 13.7; APCI MS *m/z* 246 (M + 1); Anal. ($C_{16}H_{24}ClNO.1/6H_2O$) C, H, N, Cl.

*Example 39*

O-2440 and O-2442 **(1*R*)-2-Pyrrolidin-1-yl-1-*p*-tolyl-pentan-1-one, hydrogen chloride salt (O-2440) and (1*S*)-2-Pyrrolidin-1-yl-1-*p*-tolyl-pentan-1-one, hydrogen chloride salt** (O-2442). Pyrovalerone.HCl (10.0 g, 35.5 mmol) was freed from its hydrogen chloride salt by extraction into $Et_2O$ from 20% aqueous $Na_2CO_3$ at pH 8-9. The free base was dissolved in EtOH (50 mL) and heated until nearly boiling. Dibenzoyl-D-tartaric acid (12.7 g, 35.5 mmol) in hot ethanol (150 mL) was added all at once to the pale yellow solution of free base. The resulting colorless solution was refluxed for 1 min, cooled, and the solvent was removed *in vacuo*. The residue was dissolved in $CH_2Cl_2$ (530 mL) and hexanes (700 mL) were added with swirling. After 3 d, the resulting crystalline solid (9.1 g) was collected on a frit. Analysis by $^1H$ NMR in $CDCl_3$ showed that this material had a diastereomeric excess (d.e.) of 70 - 75%. A further three recrystallizations from $CH_2Cl_2$/hexanes (300 mL/400 mL) gave a single diastereoisomer (6.1 g, 61%). Mp 100 - 120°C; $^1H$ NMR $\delta$ 8.10 (d, 4H), 7.87 (d, 2H), 7.51 (t, 2H), 7.37 (t, 2H), 7.18 (d, 2H), 5.91 (s, 2H), 5.37 (t, 1H), 3.75 (br, m, 2H), 2.32 (s, 3H), 2.0 - 1.8 (br, m, 6H), 1.4 - 1.1 (br, m, 4H), 0.71 (t, 3H). XRD analysis of this compound showed it to be a salt of dibenzoyl-D-tartaric acid and (1*R*)-2-Pyrrolidin-1-yl-1-*p*-tolyl-pentan-1-one. The dibenzoyltartarate salt was dissolved in 20% aqueous $Na_2CO_3$ and extracted into $Et_2O$. The $Et_2O$ layer was collected, dried and filtered. The hydrogen chloride salt was prepared by adding 2 M ethereal HCl to this solution. The resulting white solid was recrystallized from EtOH/$Et_2O$ to give pure (1*R*)-2-Pyrrolidin-1-yl-1-*p*-tolyl-pentan-1-one as its hydrogen chloride salt. The physical properties of this compound are identical with those of the racemic material.

The residues from recrystallization of the dibenzoyl-D-tartaric acid-(1*R*)-2-Pyrrolidin-1-yl-1-*p*-tolyl-pentan-1-one were combined and the free base was liberated by reaction with 20% aqueous $Na_2CO_3$. The ethereal extracts were washed once with 20% aqueous $Na_2CO_3$, dried ($MgSO_4$), filtered, and reduced to an oil (5.2 g, 21 mmol) *in vacuo*. This oil was taken up in hot EtOH (50 mL), and a solution of dibenzoyl-1-tartaric acid (7.5 g, 21 mmol) in hot EtOH (100 mL) was added with swirling. The mixture was refluxed for 1 min, cooled, then the solvent was

removed *in vacuo*. Four recrystallizations, as described above, gave a single diastereoisomer (5.4 g, 50%). XRD analysis showed that this material was a diastereomeric salt of dibenzoyl-1-tartaric acid-(1*S*)-2-Pyrrolidin-1-yl-1-*p*-tolyl-pentan-1-one. The hydrogen chloride salt was prepared as described above for (1*R*)-2-Pyrrolidin-1-yl-1-*p*-tolyl-pentan-1-one.

Compounds were all prepared by α-bromination of analogous ketones by the following general procedure (General Procedure B). The ketone (as a solution in $Et_2O$, or $CH_2Cl_2$ (for less soluble substrates)) was cooled on an ice bath and anhydrous $AlCl_3$ was added to the solution (catalytic quantity, 1 - 5 mol%). Bromine (approximately 0.1 mol eq) was added to the solution all at once. Typically, after 10 min the solution changed from a light orange to colorless (if this change did not occur at 0°C, then the flask was warmed to room temperature). The remaining bromine (0.9 mol eq) was then added to the solution in a drop-wise manner over 5 min. The solution was neutralized (aqueous $NaHCO_3$), separated, dried ($MgSO_4$), filtered, and reduced to a lightly colored oil *in vacuo*. Yields were quantitative and the crude materials were judged to be sufficiently pure by $^1H$ NMR for use directly in the subsequent step.

*Example 40*

**4-(2-Bromo-pentanoyl)-benzonitrile.** $^1H$ NMR $\delta$ 8.11 (d, 2H), 7.80 (d, 2H), 5.07 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.7 - 1.35 (m, 2H), 1.00 (t, 3H).

*Example 41*

**2-Bromo-1-(3,4-dimethoxy-phenyl)-pentan-1-one (x), and 2-Bromo-1-(2-bromo-4,5-dimethoxy-phenyl)-pentan-1-one.** These two compounds were produced together by General Procedure B and were separated by careful chromatography (10% EtOAc/hexanes). 2-Bromo-1-(3,4-dimethoxy-phenyl)-pentan-1-one; $^1H$ NMR $\delta$ 7.66 (dd, 1H), 7.58 (d, 1H), 6.91 (d, 1H), 5.15 (dd, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 2.25 - 2.05 (m, 2H), 1.7 - 1.35 (m, 2H), 1.01 (t, 3H). 2-Bromo-1-(2-bromo-4,5-dimethoxy-phenyl)-pentan-1-one; $^1H$ NMR $\delta$ 7.07 (s, 1H), 7.04 (s, 1H), 5.28 (dd, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 2.3 - 2.0 (m, 2H), 1.7 - 1.4 (m, 2H), 1.00 (t, 3H).

*Example 42*

**2-Bromo-4-methyl-1-*p*-tolyl-pentan-1-one.** $^1H$ NMR $\delta$ 7.92 (d, 2H), 7.29 (d, 2H), 5.21 (dd, 1H), 2.43 (s, 3H), 2.15 - 1.95 (m, 2H), 1.95 - 1.75 (m, 1H), 0.96 (d, 6H).

*Example 43*

**2-Bromo-1-(4-iodo-phenyl)-pentan-1-one.** $^1H$ NMR $\delta$ 7.85 (d, 2H), 7.72 (d, 2H), 5.06 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.65 - 1.35 (m, 2H), 0.98 (t, 3H).

*Example 44*

**2-Bromo-1-(4-trifluoromethyl-phenyl)-pentan-1-one.** $^1H$ NMR $\delta$ 8.13 (d, 2H), 7.76 (d, 2H), 5.11 (dd, 1H), 2.25 - 2.1 (m, 2H), 1.7 - 1.4 (m, 2H), 1.00 (t, 3H).

*Example 45*

**2-Bromo-1-naphthalen-2-yl-pentan-1-one.** $^1H$ NMR $\delta$ 8.55 (s, 1H), 8.1 - 7.85 (m, 4H), 7.60 (m, 2H), 5.33 (dd, 1H), 2.3 - 2.1 (m, 2H), 1.7 - 1.4 (m, 2H), 1.01 (t, 3H).

*Example 46*

**2-Bromo-1-*o*-tolyl-pentan-1-one.** 7.63 (d, 1H), 7.42 (m, 1H), 7.27 (m, 2H), 5.05 (dd, 1H), 2.25 - 2.0 (m, 2H), 1.65 - 1.35 (m, 2H), 0.99 (t, 3H).

*Example 47*

**2-Bromo-1-(4-bromo-phenyl)-pentan-1-one.** $^1H$ NMR $\delta$ 7.88 (d, 2H), 7.63 (d, 2H), 5.06 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.65 - 1.35 (m, 2H), 0.99 (t, 3H).

*Example 48*

***N*-[4-(2-Bromo-pentanoyl)-phenyl]-acetamide.** $^1H$ NMR $\delta$ 8.00 (d, 2H), 7.65 (br, m, 3H), 5.12 (dd, 1H), 2.23 (s, 3H), 2.2 - 2.05 (m, 2H), 1.7 - 1.35 (m, 2H), 0.98 (t, 3H).

*Example 49*

**4-(2-Bromo-pentanoyl)-benzoic acid methyl ester.** $^1H$ NMR $\delta$ 8.14 (d, 2H), 8.06 (d, 2H), 5.13 (t, 1H), 3.96 (s, 3H), 2.2 - 2.05 (m, 2H), 1.65 - 1.35 (m, 2H), 1.00 (t, 3H).

*Example 50*

**2-Bromo-1-(4-hydroxymethyl-phenyl)-pentan-1-one.** $^1H$ NMR $\delta$ 8.01 (d, 2H), 7.48 (d, 2H), 5.15 (dd, 1H), 4.79 (br, d, 2H), 2.25 - 2.05 (m, 2H), 2.05 - 1.95 (br, 1H), 1.65 - 1.4 (m, 2H), 0.99 (t, 3H).

*Example 51*

**2-Bromo-1-(4-fluoro-phenyl)-pentan-1-one.** $^1H$ NMR $\delta$ 8.05 (dd, 2H), 7.16 (dd, 2H), 5.09 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.7 - 1.35 (m, 2H), 0.99 (t, 3H).

*Example 52*

**2-Bromo-1-phenyl-pentan-1-one.** $^1H$ NMR $\delta$ 8.02 (d, 2H), 7.62 (m, 1H), 7.49 (t, 2H), 5.15 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.7 - 1.4 (m, 2H), 0.99 (t, 3H).

*Example 53*

**2-Bromo-1-(3,4-dichloro-phenyl)-butan-1-one.** $^1$H NMR $\delta$ 8.09 (d, 1H), 7.84 (dd, 1H), 7.57 (d, 1H), 4.95 (dd, 1H), 2.35 - 2.05 (m, 2H), 1.09 (t, 3H).

*Example 54*

**2-Bromo-1-(3,4-dichloro-phenyl)-pentan-1-one.** $^1$H NMR $\delta$ 8.09 (d, 1H), 7.84 (dd, 1H), 7.55 (d, 1H), 5.02 (dd, 1H), 2.25 - 2.05 (m, 2H), 1.65 - 1.35 (m, 2H), 0.99 (t, 3H).

*Example 55*

**2-Bromo-1-*p*-tolyl-pentan-1-one.** $^1$H NMR $\delta$ 7.92 (d, 2H), 7.29 (d, 2H), 5.14 (dd, 1H), 2.43 (s, 3H), 2.25 - 2.05 (m, 2H), 1.65 - 1.35 (m, 2H), 0.98 (t, 3H)

*Example 56*

**2-Bromo-1-(4-methoxy-phenyl)-pentan-1-one.** $^1$H NMR $\delta$ 8.01 (d, 2H), 6.96 (d, 2H), 5.12 (dd, 1H), 3.89 (s, 3H), 2.25 - 2.05 (m, 2H), 1.65 - 1.35 (m, 2H), 0.98 (t, 3H).

The ketones were prepared (except where noted) by alkylation of the analogous commercially available nitrile compounds, followed by acidic hydrolysis by the following method (General Procedure C). The nitrile (10 mmol) was added in several portions, over 0.5 h to a solution of the $^n$BuMgCl (12 mmol) in toluene (20 mL). The reactions were monitored by TLC and heated where necessary. Generally, after 2 h stirring at room temperature, the reaction was complete. The reaction mixture was poured onto ice and concentrated $H_2SO_4$ (2 mL) was added. Hydrolysis of the intermediate imine usually occurred at room temperature after several minutes, however, for some substrates, heating was necessary to effect this transformation. The organics were extracted into $Et_2O$, dried ($MgSO_4$), filtered, and reduced to an oil *in vacuo*.

*Example 57*

**N-(4-Pentanoyl-phenyl)-acetamide.** Acetanilide (15.0 g, 111 mmol) was taken up in $CS_2$ and valeryl chloride (22.5 g, 186 mmol) was added in one portion. $AlCl_3$ (44 g, 330 mmol) was added in 2 g portions to the resulting solution over a period of 0.5 h. The translucent mixture was heated to reflux for 18 h. On cooling, the top layer of $CS_2$ was decanted from the remaining brown oil which was subsequently poured onto ice containing concentrated HCl (10 mL). The resulting gummy orange solid was collected by filtration, washed with saturated aqueous $NaHCO_3$, then a small volume of $Et_2O$ and dried in air. Recrystallization from hot MeOH gave pure N-(4-Pentanoyl-phenyl)-acetamide (14.7 g, 60%) as a colorless solid. $^1$H NMR $\delta$ 7.94 (d, 2H), 7.61 (d, 2H), 7.41 (br, s, 1H), 2.94 (t, 2H), 2.22 (s, 3H), 1.8 - 1.65 (m, 2H),

1.45 - 1.35 (m, 2H), 0.95 (t, 3H); $^{13}$C NMR $\delta$ 168.4, 142.0, 132.9, 129.5, 118.8, 38.2, 26.6, 24.8, 22.5, 14.0.

*Example 58*

**1-(3,4-Dichloro-phenyl)-pentan-1-one.** Following General Procedure C, this compound was prepared in 93% yield and employed in the next step of the reaction as the crude material. $^{1}$H NMR $\delta$ 8.03 (d, 1H), 7.78 (dd, 1H), 7.54 (d, 1H), 2.92 (t, 2H), 1.71 (m, 2H), 1.39 (m, 2H), 0.94 (t, 3H).

*Example 59*

**1-(3,4-Dichloro-phenyl)-butan-1-one.** Following General Procedure C, this compound was prepared in 100% yield and employed in the next step of the reaction as the crude material $^{1}$H NMR $\delta$ 8.01 (d, 1H), 7.78 (dd, 1H), 7.54 (d, 1H), 2.91 (t, 2H), 1.77 (sextet, 2H), 1.01 (t, 3H).

*Example 60*

**1-(3,4-Dimethoxy-phenyl)-pentan-1-one.** This compound was prepared following General Procedure C. The crude material was further purified by distillation (Bp 131 °C, 0.05 mmHg) to give the pure title compound in 80% yield. $^{1}$H NMR $\delta$ 7.60 (dd, 1H), 7.54 (d, 1H), 6.89 (d, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.93 (t, 2H), 1.72 (m, 2H), 1.42 (m, 2H), 0.96 (t, 3H).

*Example 61*

**4-Methyl-1-*p*-tolyl-pentan-1-one.** This compound was prepared in quantitative yield by Friedel Crafts acylation of toluene with valeryl chloride. $^{1}$H NMR $\delta$ 7.86 (d, 2H), 7.26 (d, 2H), 3.94 (t, 2H), 2.41 (s, 3H), 1.62 (m, 3H), 0.94 (d, 6H).

*Example 62*

**1-(4-Trifluoromethyl-phenyl)-pentan-1-one.** Following General Procedure C, this compound was prepared in 95% yield and employed in the next step of the reaction as the crude material. $^{1}$H NMR $\delta$ 8.06 (d, 2H), 7.43 (d, 2H), 3.00 (t, 2H), 1.74 (m, 2H), 1.41 (m, 2H), 0.96 (t, 3H).

*Example 63*

**1-Naphthalen-2-yl-pentan-1-one.** Following General Procedure C, this compound was prepared in 95% yield and employed in the next step of the reaction as the crude material. $^{1}$H NMR $\delta$ 8.48 (s, 1H), 8.04 (dd, 1H), 7.97 (d, 1H), 7.90 (m, 2H), 7.57 (m, 2H), 3.11 (t, 2H), 1.79 (m, 2H), 1.44 (m, 2H), 0.98 (t, 3H).

*Example 64*

**1-(3,4-Dichloro-phenyl)-pen-2-en-1-one.** 2-Bromo-1-(3,4-dchloro-phenyl)-pentan-1-one (x) (3.36 g, 10.9 mmol) was dissolved in DMF (60 mL). $Li_2CO_3$ (1.28 g, 17 mmol) and LiBr (0.99 g, 11.5 mmol) was added to the solution which was then heated with stirring to 110 - 120 °C (oil bath temperature) for 1.5 h. The mixture was diluted with $H_2O$ (100 mL) and the organics were extracted into EtOAc (3 x 50 mL). The ethyl acetate layer was collected and washed with saturated brine (2 x 50 mL), dried ($MgSO_4$), filtered, and reduced to an oil *in vacuo.* Careful column chromatography (1% EtOAc/hexanes - 2.5% EtOAc/hexanes) furnished the pure compound as a colorless solid (1.5 g, 60%). $^1$H NMR $\delta$ 8.01 (d, 1H), 7.76 (dd, 1H), 7.55 (d, 1H), 7.15 (dt, 1H), 6.80 (dt, 1H), 2.37 (m, 2H), 1.15 (t, 3H); $^{13}$C NMR $\delta$ 188.5, 152.8, 137.6, 137.1, 133.2, 130.6, 130.5, 127.5, 124.1, 26.0, 12.2.

*Example 65*

**1-*p*-Tolyl-pent-2-en-1-one.** This compound was prepared as described for (x) employing 2-Bromo-1-*p*-tolyl-pentan-1-one (x) as a starting material. The yield was 82%. $^1$H NMR $\delta$ 7.85 (d, 2H), 7.25 (d, 2H), 7.10 (dt, 1H), 6.88 (dt, 1H), 2.39 (s, 3H), 2.32 (m, 2H), 1.13 (t, 3H); $^{13}$C NMR $\delta$ 190.3, 150.6, 143.2, 135.3, 129.0, 128.5, 124.7, 25.7, 21.5, 12.2.

*Example 66*

**1-(3-Iodo-phenyl)-pentan-1-one.** This compound was prepared according to General Procedure C and was purified by column chromatography (3% EtOAc/hexanes). The yield was 29%. $^1$H NMR $\delta$ 8.28 (t, 1H), 7.90 (m, 2H), 7.21 (t, 3H), 2.93 (t, 2H), 1.71 (m, 2H), 1.40 (m, 2H), 0.96 (t, 3H); $^{13}$C NMR $\delta$ 199.1, 141.6, 138.8, 137.0, 130.3, 127.1, 94.4, 38.3, 26.2, 22.4, 13.9.

*Example 67*

**1-(4-Iodo-phenyl)-pentan-1-one.** This compound was prepared in very low yield by following General Procedure C. Friedel Crafts acylation of iodobenzene employing the "Perrier Method" (JCS P1 2493, 1973) gave a mixture of compounds. The crude compound could be distilled from this mixture (Bp 112°C, 0.1 mmHg) and further purified by recrystallization from EtOH. The yield was 11%. $^1$H NMR $\delta$ 7.82 (d, 2H), 7.67 (d, 2H), 2.92 (t, 2H), 1.71 (m, 2H), 1.40 (m, 2H), 0.95 (t, 3H).

*Example 68*

**1-*o*-Tolyl-pentan-1-one.** This compound was prepared following General Procedure C and was purified by distillation (Bp 58 - 60°C, 0.05 mmHg). The yield was 75%. $^1$H NMR $\delta$

7.62 (m, 1H), 7.36 (m, 1H), 7.26 (m, 2H), 2.89 (t, 2H), 2.48 (s, 3H), 1.68 (m, 2H), 1.39 (m, 2H), 0.94 (t, 3H).

*Example 69*

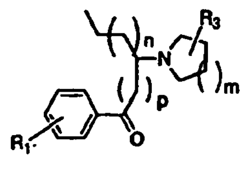
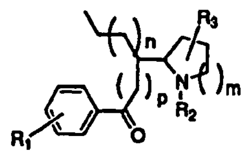
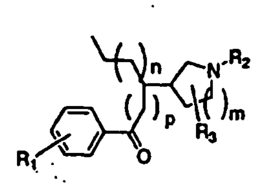
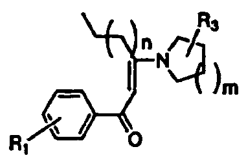
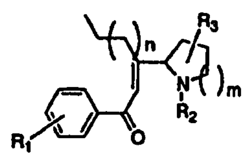
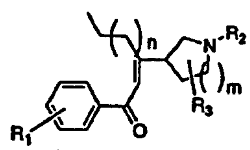
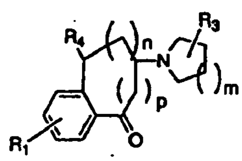
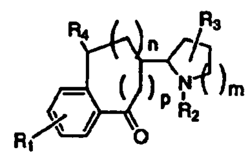
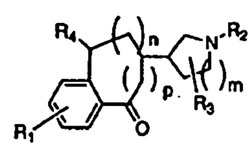
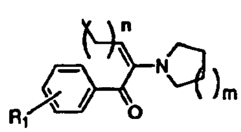
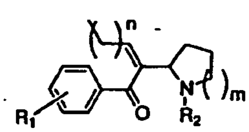
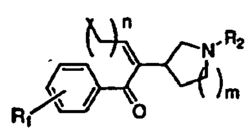
**1-m-Tolyl-pentan-1-one.** This compound was prepared following General Procedure C and was purified by distillation (Bp 64 - 68°C, 0.1 mmHg). The yield was 98% $^{1}$H NMR $\delta$ 7.86 (d, 2H), 7.26 (d, 2H), 2.94 (t, 2H), 2.41 (s, 3H), 1.71 (m, 2H), 1.41 (m, 2H), 0.95 (t, 3H).

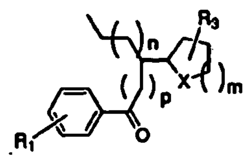
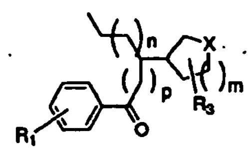
The present invention has been described in detail, including the preferred embodiments thereof. However, it will be appreciated that those skilled in the art, upon consideration of the present disclosure, may make modifications and/or improvements of this invention and still be within the scope and spirit of this invention as set forth in the following claims.

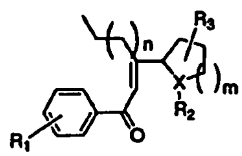
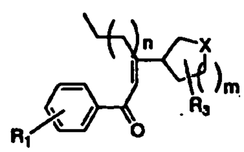
All references cited are incorporated herein in their entirety by reference.

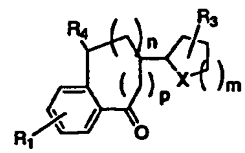
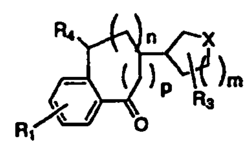
What we claim:

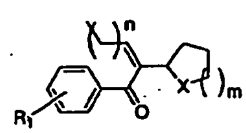
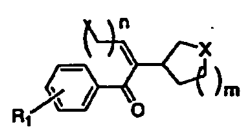
1. A compound having any one of the following formulae:

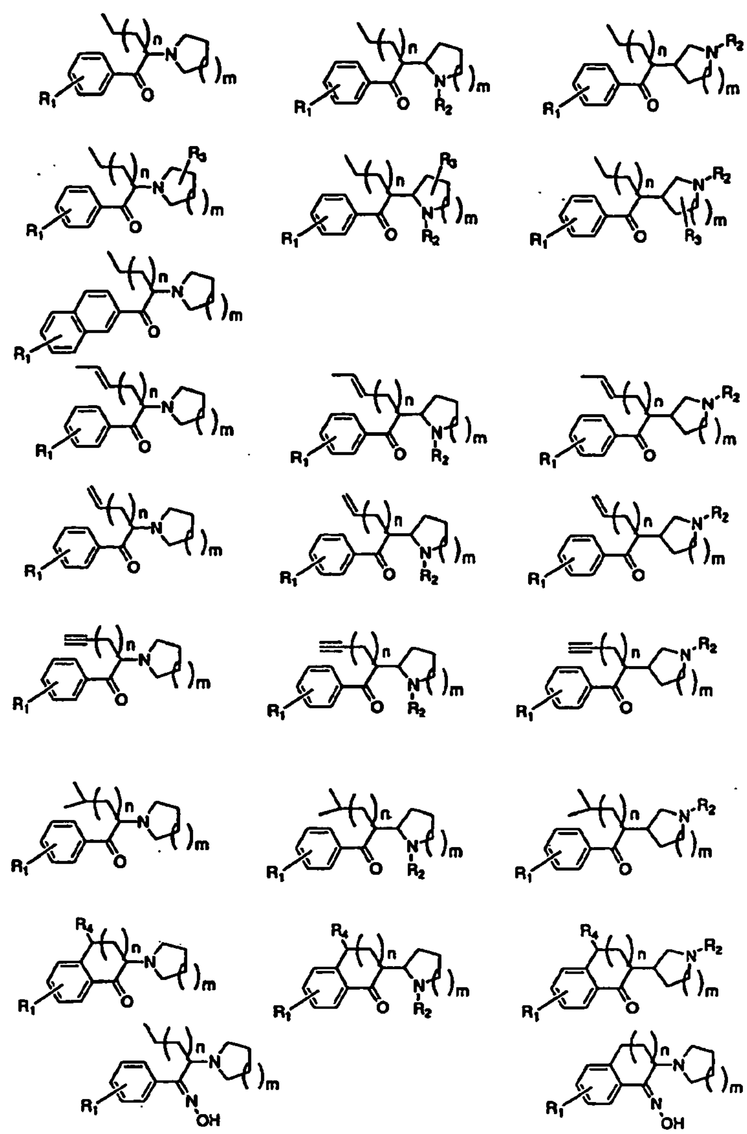













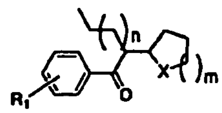
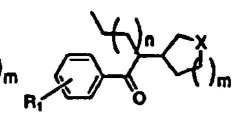
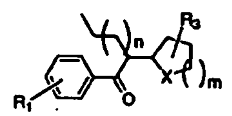



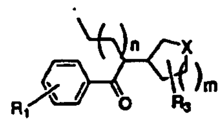
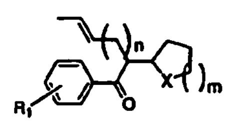
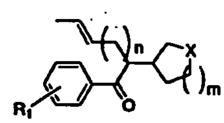



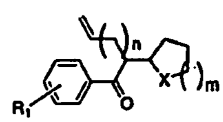
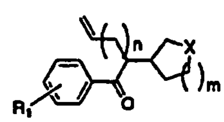
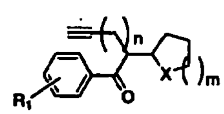



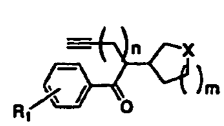
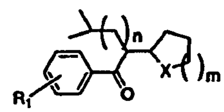
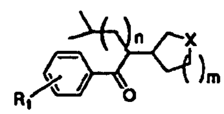


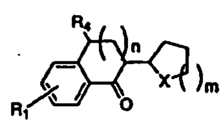
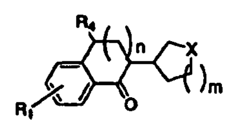
R1
R2
R3
R4
n
m
N
O
N-OH

wherein,

$R_1$ = H; Br; Cl; I; F; OH; $OCH_3$; $CF_3$; $NO_2$; $NH_2$; CN; $NHCOCH_3$; $C(CH_3)_3$; $C(CH_2)CH_3$; $(CH_2)_qCH_3$ where q=0-6; $COCH_3$; alkyl; alkenyl; alkynyl; allyl; isopropyl; isobutyl; F (at the 2, 3 or 4 position); Cl (at the 2, 3 or 4 position); I (at the 2, 3 or 4 position) 3,4-diCl; 3-C1,4-$C(CH_2)CH_3$; 3-Br,4-$C(CH_2)CH_3$; 3-I,4-$C(CH_2)CH_3$; 4-C1,3-$C(CH_2)CH_3$; 4-Br,3-$C(CH_2)CH_3$; 4-I,3-$C(CH_2)CH_3$; 3,4-diOH; 3,4-diOAc; 3,4-di$OCH_3$; 3-OH,4-Cl; 3-OH,4-F; 3-C1,4-OH; 3-F,4-OH; $CH_2OH$; $CH_2OCH_3$; $CH_2000CH_3$;

$CH_2OR_2$; $(CH_2)_{,,}000R_2$; $(CH_2)_nOR_2$;$(CH_2)_nOCOR_2$; and,

$R_2$ = alkyl; alkenyl; alkynyl; allyl; isopropyl; isobutyl; H; $CH_3$; $CH_2ArR_1$; $(CH_2)_{n,}$Ar(phenyl or naphthyl)$R_1$; and,

$R_3$ = alkyl; alkenyl; alkynyl; allyl; isopropyl; isobutyl; H; $CH_3$; $CH_2ArR_1$; $(CH_2)_nArR_1$; H; Br; Cl; I; F; OH; $OCH_3$; $CF_3$; $NO_2$; $NH_{2;}$ CN; $NHCOCH_3$; $C(CH_3)_3$; $C(CH_2)CH_3$; $(CH_2)qCH_3$ where q=0-6; $COCH_3$; $CH_2OH$; $CH_2OCH_3$; $CH_2OCOCH_3$; $CH_2OR_2$; $(CH_2)_nOCOR_2$; $(CH_2).OR_2$; $(CH_2)_n$ $OCOR_2$; and,

N = 0 - 4; and,

m, p = 0 - 2; and,

X = O, $CH_2$, S, $SO_2$, SO.

2. The compounds of claim 1, wherein the compounds are a 2-S enantiomer.

3. The compounds of claim 1, wherein the compounds bind and/or inhibit monoamine transporters of mammalian systems.

4. The compounds of claim 3, wherein the monoamine transporters are dopamine transporters of mammalian systems.

5. The compounds of claim 3, wherein the monoamine transporters are serotonin transporters of mammalian systems.

6. The compounds of claim 3, wherein the monoamine transporters are norepinephrine transporters of mammalian systems.

7. The compounds of claim 3, wherein two or more compounds are used in combination to inhibit monoamine transporters.

8. The compounds of claim 1, wherein $IC_{50}$ SERT/DAT ratio is greater than about 10, preferably greater than about 30 and more preferably 50 or more.

9. The compounds of claim 1, having an $IC_{50}$ at the DAT of less than about 500 nM, preferably less than 60 nM, more preferably less than about 20 nM, and most preferably less than about 10 nM.

10. The compounds of claim 1, wherein any one of the compounds are used to treat neurochemical disorders related to monoamine neurotransmitter uptake systems.

11. The compounds of claim 10, wherein the neurochemical disorders are Parkinson's disease, Attention Deficit Disorder, depression, cognition, Alzheimer's disease, Obsessive Compulsive Disorder, Tourette's Syndrome, schizophrenia, psychosis.

12. A method for inhibiting 5-hydroxytryptamine reuptake of a monoamine transporter comprising contacting the monoamine transporter with a compound of claim 1.

13. The method of claim 12, wherein the monoamine transporter is selected from the group consisting of a dopamine transporter, a serotonin transporter and a norepinephrine transporter.

14. A method for inhibiting 5-hydroxytryptamine reuptake of a monoamine transporter in a mammal comprising administering to the mammal a 5-hydroxytryptamine reuptake inhibiting amount of a compound of claim 1.

15. A method for inhibiting dopamine reuptake of a dopamine transporter in a mammal comprising administering to the mammal a dopamine reuptake inhibiting amount of a compound of claim 1.

16. A method for inhibiting serotonin reuptake of a serotonin transporter in a mammal comprising administering to the mammal a serotonin reuptake inhibiting amount of a compound of claim 1.

17. A method for inhibiting norepinephrine reuptake of a norepinephrine transporter

in a mammal comprising administering to the mammal a norepinephrine reuptake inhibiting amount of a compound of claim 1.

18. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

19. A method for treating a mammal having a disorder selected from neurodegenerative disease, psychiatric dysfunction, dopamine dysfunction, cocaine abuse and clinical dysfunction comprising administering to the mammal an effective amount of any one of the compounds of claim 1.

20. A method for treating a mammal having a disorder selected from neurodegenerative disease, psychiatric dysfunction, dopamine dysfunction, cocaine abuse and clinical dysfunction comprising administering to the mammal an effective amount of a compound of claim 1.

21. A method for treating a neurodegenerative disease in a mammal comprising administering to the mammal an effective amount of a 2-S enantiomer having the formula of any one of the compounds of claim 1.

22. A method for treating a neurodegenerative disease in a mammal comprising administering to the mammal an effective amount of a compound of claim 1.

23. The method of claim 22, wherein the neurodegenerative disease is selected from Parkinson's disease and Alzheimer's disease.

24. A method for treating psychiatric dysfunction in a mammal comprising administering to the mammal an effective amount of a compound of claim 1.

25. The method according to claim 24, wherein the psychiatric disorder comprises depression.

26. A method for treating dopamine related dysfunction in a mammal comprising administering to the mammal a dopamine reuptake inhibiting amount of any one of the compounds of claim 1.

27. The method according to claim 26, wherein the dopamine related dysfunction comprises Attention deficit disorder.

28. A method for treating serotonin related dysfunction in a mammal comprising administering to the mammal a serotonin reuptake inhibiting amount of any one of the compounds of claim 1.

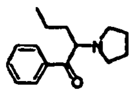
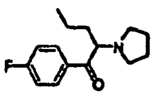
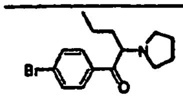
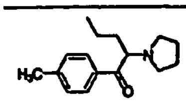
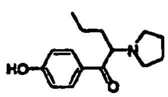
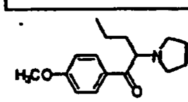
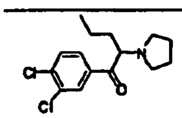
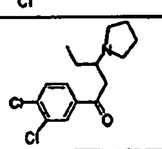
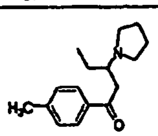
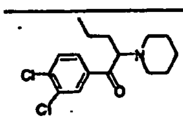
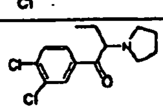
29. The method according to claim 28, wherein the serotonin related dysfunction relates to depression.

30. A method for treating clinical dysfunction in a mammal comprising administering to the mammal an effective amount of a compound of claim 1.

ABSTRACT

New tropane analogs that bind to monoamine transporters are described. The compounds of the present invention can be racemic or pure *S*-enantiomers. Certain preferred compounds of the present invention have a high selectivity for the DAT versus the SERT. Preferred monoamine transporters for the practice of the present invention include the dopamine transporter, the serotonin transporter and the norepinephrine transporter.

# FIGURE 1

| | CPD | DAT Ki<br>RTI-55 DAT Cells | SERT Ki<br>RTI-55 SERT Cells | NET Ki<br>RTI-55 NET Cells |
|---|---|---|---|---|
|  | O-2387 | 33.7 ± 6.4<br>Uptake: 52.3 ± 8.2 | >10,000 | 199 ± 45<br>Uptake 56 ± 13 |
|  | O-2370 | 82 ± 25<br>Uptake: 185 ± 62 | >10,000 | 830 ± 140<br>Uptake: 171 ± 35 |
|  | O-2419 | 51.0 ± 6.7<br>Uptake: 39.5 ± 7.5 | 830 ± 190<br>Uptake: 1050 ± 90 | 388 ± 53<br>Uptake: 83 ± 30 |
|  | O-2371 | 21.4 ± 4.6<br>Uptake : 52 ± 20 | 3770 ± 560<br>Uptake : 2780 ± 590 | 195 ± 26<br>Uptake : 28.3 ± 8.1 |
| | O-2440-R | 1330 ± 300<br>Uptake : 1790 ± 320 | >10,000 | >10,000 |
| in R | O-2442-S | 18.1 ± 3.0<br>Uptake: 16.3 ± 2.3 | 2220 ± 550<br>Uptake : 1070 ± 230 | 109 ± 45<br>Uptake: 11.3 ± 2.4 |
|  | O-2418 | 125 ± 23<br>Uptake: 49.7 ± 3.4 | >10,000 | 1290 ± 460<br>Uptake: 88.7 ± 7.5 |
|  | O-2417 | 329 ± 33<br>Uptake : 283 ± 66 | 4080 ± 410<br>Uptake: 2430 ± 720 | 2600 ± 1000<br>Uptake 235.0 ± 8.7 |
|  | O-2390 | 11.5 ± 1.4<br>Uptake : 43 ± 20 | 199 ± 50<br>Uptake : 600 ± 63 | 37.8 ± 3.2<br>Uptake : 21.0 ± 0.58 |
|  | O-2524 | 8,440 ± 310<br>Uptake : >10μM | 3,900 ± 1,00(<br>Uptake : 1,780 ± 220 | >10μM |
|  | O-2525 | >10μM | >10μM | >10μM |
|  | O-2388 | 144 ± 48<br>Uptake: 668 ± 89 | 2460 ± 260<br>Uptake : >10000 | 2350 ± 230<br>Uptake: 800 ± 200 |
|  | O-2384 | 28.8 ± 2.1<br>Uptake: 55 ± 12 | 810 ± 150<br>Uptake: 441 ± 12 | 262 ± 38<br>Uptake: 18.5 ± 804 |

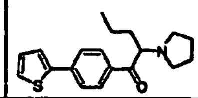
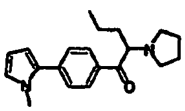
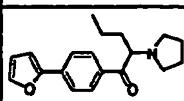
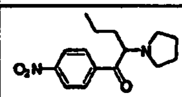
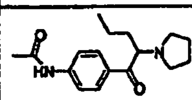
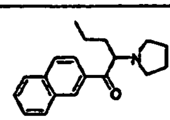
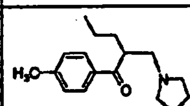
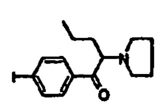
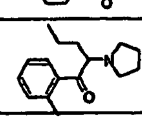
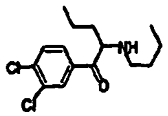
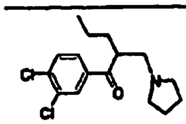
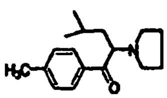
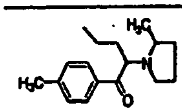
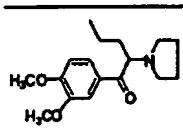
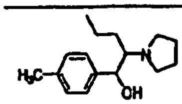
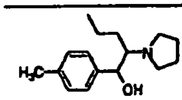
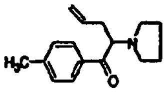
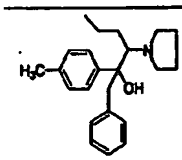
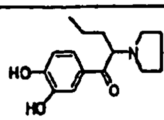
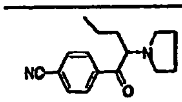
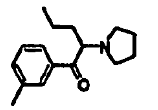
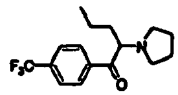
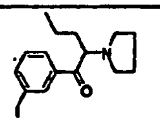
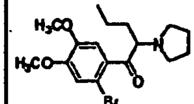
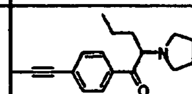
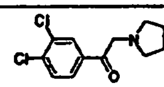
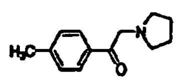
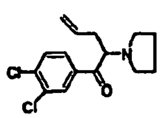
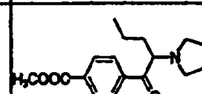
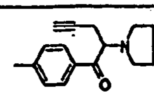
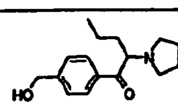
| | CPD | DAT Ki<br>RTI-55 DAT Cells | SERT Ki<br>RTI-55 SERT Cells | NET Ki<br>RTI-55 NET Cells |
|---|---|---|---|---|
|  | O-2438 | 460 ± 120<br>Uptake: 539 ± 69 | 3320 ± 280<br>Uptake : 1860 ± 720 | 370 ± 160<br>Uptake: 263 ± 94 |
|  | O-2446 | 3850 ± 330<br>Uptake: 5400 ± 1600 | >10,000 | >10,000 |
|  | O-2441 | 106 ± 17<br>Uptake: 122 ± 18 | 3330 ± 1200<br>Uptake : 2180 ± 440 | 95 ± 20<br>Uptake: 93 ± 38 |
|  | O-2443 | 268 ± 32<br>Uptake: 1110 ± 340 | 2480 ± 290<br>Uptake: 1110 ± 450 | 2690 ± 530<br>Uptake: 531 ± 67 |
|  | O-2439 | 30.2 ± 2.0<br>Uptake : 67.9 ± 8.4 | >10,000 | 4,000 ± 1,100<br>Uptake : 317 ± 64 |
|  | O-2482 | 20.1 ± 7.1<br>Uptake : 40 ± 13 | 33.1 ± 1.1<br>Uptake : 46.0 ± 5.5 | 136 ± 27<br>Uptake : 11.67 ± 0.88 |
|  | O-2477 | >10,000 | 4,100 ± 1,80(<br>Uptake: 4,800 ± 1.200 | >10,000 |
|  | O-2493 | 81.4 ± 9.2<br>Uptake: 32 ± 11 | 301 ± 26<br>Upotake: 197 ± 35 | 310 ± 34<br>Uptake: 46.5 ± 8.4 |
|  | O-2470 | 59.7 ± 9.0<br>Uptake: 63 ± 19 | 3.720 ± 520<br>Uptake: 2.020 ± 670 | 425 ± 63<br>Uptake: 19.7 ± 3.3 |

FIGURE 1 (continued)

| | | | | |
|---|---|---|---|---|
|  | O-2389 | 520 ± 110<br>Uptake: 1192 ± 58 | 5075 ± 63<br>Uptake: > 10,000 | 4200 ± 1200<br>Uptake: 2520 ± 190 |
|  | O-2478 | 1,530 ± 520<br>Uptake: 2,900 ± 1,300 | 630 ± 110<br>Uptake: 710 ± 170 | >10,000 |
|  | O-2484 | 13.7 ± 3.0<br>Uptake: 5.9 ± 2.3 | 2874.0 ± 7.6<br>Uptake: 2040 ± 150 | 259 ± 79<br>Uptake: 18.0 ± 5.0 |
|  | O-2511 | | | |
|  | O-2512 | >10,000 | 7460 ± 770<br>Uptake: 1540 ± 220 | >10,000 |
|  | O-2529 | >10 mM | 2,020 ± 550<br>Uptake: 560 ± 170 | >10 mM |
|  | O-2530 | | | |
|  | O-2556 | 90.5 ± 3.1<br>Uptake: 55 ± 17 | >10,000 | 1,400 ± 370<br>Uptake: 88 ± 16 |
|  | O-2555 | >100,000 | >10,000 | >10,000 |
|  | O-2574 | | | |
|  | O-2575 | 5900 ± 1100<br>Uptake: 1000 ± 170 | >10,000 | >10,000 |
|  | O-2480 | 51 ± 14<br>Uptake: 62.9 ± 6.9 | 5,900 ± 1,600<br>Uptake: 4,400 ± 1,100 | 216 ± 38<br>Uptake: 9.37 ± 0.82 |
|  | O-2481 | >10μM | 959 ± 82<br>Uptake: 1,030 ± 340 | >10 μM |
|  | O-2495 | | | |
|  | O-2536 | | | |
|  | O-2537 | | | |
|  | O-2538 | | | |
|  | O-2539 | | | |
|  | O-2557 | 39.9 ± 5.5<br>Uptake: 18.3 ± 3.7 | 1,080 ± 170<br>Uptake: 440 ± 170 | 509 ± 99<br>Uptake: 24.9 ± 8.2 |
|  | O-2558 | 360 ± 140<br>Uptake: 154 ± 50 | 3,950 ± 690<br>Uptake: 2,350 ± 560 | 1,140 ± 320<br>Uptake: 22.8 ± 3.3 |
|  | O-2576 | | | |
|  | O-2577 | 48.7 ± 2.2<br>Uptake: 44.3 ± 8.4 | >10,000 | 150 ± 23<br>Uptake: 12.4 ± 2.8 |

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